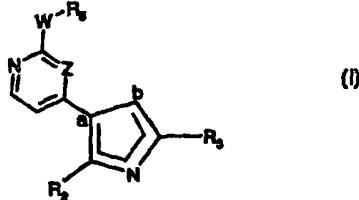


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| (54) Title:  | SUBSTITUTED AZOLES   |  |   |
| (57) Abstract  | <p>Compounds of formula (I) wherein the symbols have meaning as defined herein, are p38 MAP kinase inhibitors, and are useful pharmaceutically for treating TNF<math>\alpha</math> and IL-1 mediated diseases, such as rheumatoid arthritis, and diseases of bone metabolism, e.g. osteoporosis.</p>  <p style="text-align: center;">(I)</p> |  |   |

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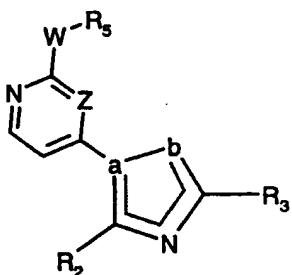
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SUBSTITUTED AZOLES

This invention relates to substituted azoles and to their use for treating TNF $\alpha$  and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

Accordingly the present invention provides a compound of formula I



wherein

a is N or C;

b is CH when a is N, or O when a is C;

$\equiv$  denotes a single or a double bond dependent upon whether the azole ring is an imidazole or an oxazole ring;

Z is N or CH;

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1-3</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond ;

R<sub>2</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, or NH<sub>2</sub> which is optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub> alkyl substituted;

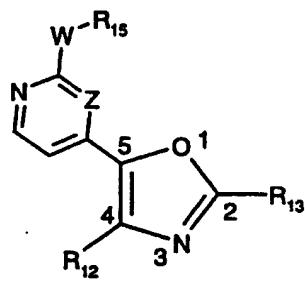
R<sub>3</sub> is H, halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or methyleneaminoguanidinyl (i.e. -CH=N-NH-C(NH).NH<sub>2</sub>), each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted

carbonyl, optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom; R<sub>5</sub> is C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or C<sub>3</sub>-C<sub>12</sub>cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,  
and esters thereof and acid addition salts thereof.

Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F.

In a particular embodiment the invention provides a 4-phenyl-5-[(2-substituted)-4-pyrimidyl or -pyridyl]-oxazole of formula I, or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof (wherein the numbering of the atoms of the oxazole ring is shown below in formula II.)

Thus in a particular embodiment the invention provides a compound of formula II



II

wherein

Z is N or CH;

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond;

R<sub>12</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, or NH<sub>2</sub> which is optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub> alkyl substituted;

R<sub>13</sub> is H, halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or methyleneaminoguanidinyl (i.e. -CH=N-NH-C(NH).NH<sub>2</sub>), each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom;

R<sub>15</sub> is C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or C<sub>3</sub>-C<sub>12</sub>cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

When R<sub>13</sub> is heteroaryl it is preferably pyridyl (e.g. 4-pyridyl) or pyrimidyl, each optionally substituted, e.g. by up to 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino.

When R<sub>13</sub> is cycloalkyl it is preferably C<sub>3</sub>-C<sub>8</sub>, especially C<sub>5</sub>-C<sub>6</sub>cycloalkyl (e.g. cyclohexyl), optionally substituted, e.g. by 1 or 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino.

When R<sub>13</sub> is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, e.g. N or O, and is optionally substituted, e.g. by 1 or 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino.

When  $R_{15}$  is aryl it is preferably phenyl. When  $R_{15}$  is cycloalkyl, it is preferably  $C_3$ - $C_7$  cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl.  $R_{15}$  may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen,  $C_1$ - $C_{10}$ alkyl, halo-substituted  $C_1$ - $C_{10}$ alkyl,  $C_1$ - $C_{10}$ alkoxy, hydroxy or  $-NR_7R_8$ , where  $R_7$  and  $R_8$  are independently H,  $C_1$ - $C_6$ alkyl,  $C_6$ - $C_{10}$ aryl,  $C_6$ - $C_{10}$ heteroaryl,  $C_7$ - $C_{11}$ aralkyl or  $C_7$ - $C_{11}$ heteroaralkyl.

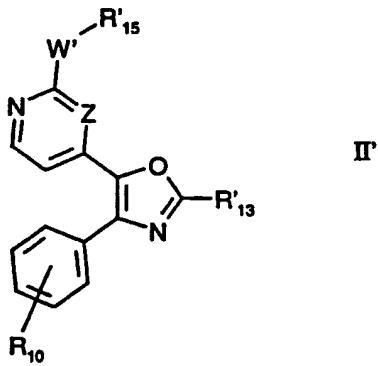
When Y is  $C_1$ - $C_4$  alkylene, it is preferably  $C_1$ - $C_2$  alkylene, and is optionally substituted, e.g. by  $C_1$ - $C_4$ alkyl (e.g. methyl), halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, or amino.

More preferably  $R_{12}$  is phenyl substituted, preferably mono- or di-substituted, by halogen or a halogen-containing group, e.g. 4-fluorophen-1-yl, or 3- $CF_3$ , 3-Cl, or 3,4-difluoro substituted.

More preferably  $R_{13}$  is H,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_4$ alkenyl, phenyl, pyridyl, morpholinyl, piperidinyl, piperazinyl, or N-mono- or di- $C_1$ - $C_4$ alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, or optionally mono-or di-N- $C_1$ - $C_4$ alkyl substituted amino.

Preferably W is  $-NH-Y'$ -,  $-O-$  or  $-S-$ , where  $Y'$  is  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH(CH_3)-$  or a direct bond

Thus in preferred embodiments the invention provides a compound of formula II'



wherein

$R_{15}'$  is phenyl or  $C_3$ - $C_7$ cycloalkyl each of which is optionally mono-substituted by halogen,  $C_1$ - $C_{10}$ alkyl,  $C_1$ - $C_{10}$ alkoxy, hydroxy, trihalomethyl or  $-NR_7R_8$ , where  $R_7$  and  $R_8$  are independently H,  $C_1$ - $C_6$ alkyl,  $C_6$ - $C_{10}$ aryl,  $C_6$ - $C_{10}$ heteroaryl,  $C_7$ - $C_{11}$ aralkyl or  $C_7$ - $C_{11}$ heteroaralkyl;

$R_{10}$  is halogen,  $CF_3$ , cyano, amido, thioamido, amino  $C_1$ - $C_6$ alkyl;

$R_{13}'$  is H,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_4$ alkenyl, phenyl, pyridyl, morpholinyl, piperidinyl, piperazinyl, or N-mono- or di- $C_1$ - $C_4$ alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, or optionally mono-or di-N- $C_1$ - $C_4$ alkyl substituted amino;

$Z$  is N or CH and

$W'$  is  $-NH-Y'$ -,  $-O-$  or  $-S-$ , where  $Y'$  is  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH(CH_3)-$  or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably  $R_{15}'$  is unsubstituted or monosubstituted by halogen,  $C_1$ - $C_4$ alkyl (e.g. methyl),  $C_1$ - $C_4$ alkoxy (e.g. methoxy), hydroxy or  $CF_3$ .

Preferably  $R_{10}$  is halogen, e.g. F, or  $CF_3$ .

Preferably  $R_{13}'$  is  $C_1$ - $C_6$ alkyl, morpholinyl, piperidinyl, piperazinyl, or N-mono- or di- $C_1$ - $C_4$ alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by hydroxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, or amino.

Preferably  $W'$  is  $-NH-Y'$ -, where  $-Y'$  is  $-CH_2-$ ,  $-CH(CH_3)-$  or a direct bond.

The Invention includes the following compounds of formula II:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-morpholinylloxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-piperidinylloxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-ethoxy-carbonylpiperazin-1-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-methyl-piperidine-1-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-ethyl-piperazin-1-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N,N-diethylaminooxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-N-acetyl-piperidine-1-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-pyridyl)oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-piperazinyl) oxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-amino-1-methyl)ethyloxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-hydroxy-4-methylpiperidine-1-yl)oxazole;

4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-[cyclopropylmethyl]amino-4-pyridyl)oxazole;

4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole;

4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclopropylmethy lamino-4-pyridyl)oxazole;

4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-cyclopropylmethy lamino-4-pyridyl)oxazole;

4-(4-Fluorophenyl)-5-(2-cyclopropylmethy lamino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole;

4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidin-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole;

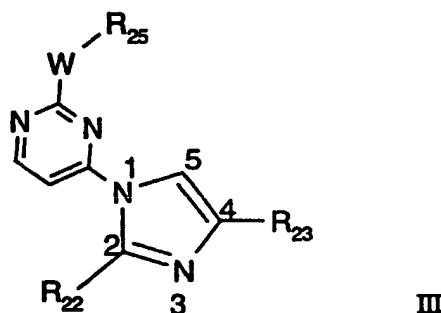
4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidin-1-yl)-5-(2-cyclopropylamino-4-pyridyl)oxazole;

4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl) xazole;

4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidin-1-yl)-5-(2-cyclopropylamino-4-pyridyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole, and  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole.

In a further particular embodiment the invention provides a 1-[(2-substituted)-4-pyrimidyl]-2-phenyl-imidazole of formula I or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof. (The numbering of the atoms of the imidazole ring is shown below in formula III.)

Thus in yet further particular embodiments the invention provides a compound of formula III



wherein

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond;

R<sub>22</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, or NH<sub>2</sub> which is optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted;

$R_{23}$  is H, halogen,  $C_1\text{-}C_{10}$ alkyl,  $C_1\text{-}C_4$ alkenyl,  $C_3\text{-}C_{10}$ cycloalkyl,  $C_3\text{-}C_{18}$ heterocycloalkyl,  $C_6\text{-}C_{18}$ aryl,  $C_3\text{-}C_{18}$ heteroaryl or methyleneaminoguanidinyl (i.e.  $-\text{CH=NH-NH-C(NH)NH}_2$ ), each of which may be optionally substituted by up to 4 substituents separately selected from  $C_1\text{-}C_4$ alkyl optionally substituted by hydroxy, halogen, halo-substituted- $C_1\text{-}C_4$ alkyl, hydroxy,  $C_1\text{-}C_4$ alkoxy,  $C_1\text{-}C_4$ alkylthio, carboxy, optionally  $C_1\text{-}C_6$ alkyl or  $C_1\text{-}C_6$ alkoxy substituted carbonyl, optionally mono-or di- $N\text{-}C_1\text{-}C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom;

$R_{25}$  is  $C_6\text{-}C_{18}$ aryl,  $C_3\text{-}C_{18}$ heteroaryl, or  $C_3\text{-}C_{12}$ cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from  $C_1\text{-}C_4$ alkyl, halogen, halo-substituted- $C_1\text{-}C_4$ alkyl, hydroxy,  $C_1\text{-}C_4$ alkoxy,  $C_1\text{-}C_4$ alkylthio, or optionally mono-or di- $N\text{-}C_1\text{-}C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

When  $R_{23}$  is aryl, it is preferably phenyl optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1\text{-}C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1\text{-}C_4$ alkoxy, carboxy, optionally  $C_1\text{-}C_6$ alkyl or  $C_1\text{-}C_6$ alkoxy substituted carbonyl, optionally mono-or di- $N\text{-}C_1\text{-}C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom.

When  $R_{23}$  is heteroaryl it is preferably pyridyl (e.g. 4-pyridyl or 3-pyridyl), pyrimidyl, thienyl, furyl, or benzofuryl, each optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1\text{-}C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1\text{-}C_4$ alkoxy, carboxy, optionally  $C_1\text{-}C_6$ alkyl or  $C_1\text{-}C_6$ alkoxy substituted carbonyl, optionally mono-or di- $N\text{-}C_1\text{-}C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom.

When  $R_{23}$  is cycloalkyl it is preferably  $C_3\text{-}C_8$ , especially  $C_3\text{-}C_6$ cycloalkyl (e.g. cyclohexyl), optionally substituted, e.g. by 1 or 2 substituents, separately selected from  $C_1\text{-}C_4$ alkyl, halogen, hydroxy,  $C_1\text{-}C_4$ alkoxy, or optionally mono-or di- $N\text{-}C_1\text{-}C_4$ alkyl substituted amino.

When  $R_{23}$  is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, e.g. N or O, and is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, optionally mono- or di-N- $C_1$ - $C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom.

When  $R_{25}$  is aryl it is preferably phenyl. When  $R_{25}$  is cycloalkyl, it is preferably  $C_3$ - $C_7$  cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl.  $R_{25}$  may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen,  $C_1$ - $C_{10}$ alkyl, halo-substituted  $C_1$ - $C_{10}$ alkyl,  $C_1$ - $C_{10}$ alkoxy, hydroxy or -NR<sub>7</sub>R<sub>8</sub>, where R<sub>7</sub> and R<sub>8</sub> are independently H,  $C_1$ - $C_6$ alkyl,  $C_6$ - $C_{10}$ aryl,  $C_6$ - $C_{10}$ heteroaryl,  $C_7$ - $C_{11}$ aralkyl or  $C_7$ - $C_{11}$ heteroaralkyl.

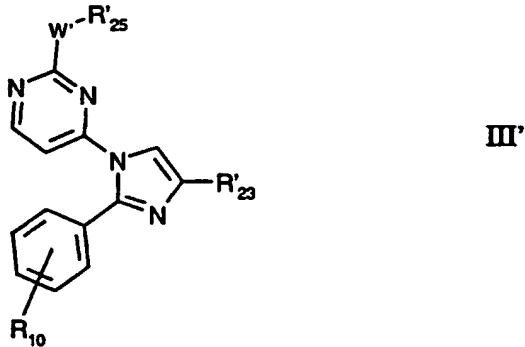
When Y is  $C_1$ - $C_4$  alkylene, it is preferably  $C_1$ - $C_2$  alkylene, and is optionally substituted, e.g. by  $C_1$ - $C_4$ alkyl (e.g. methyl), halogen, hydroxy, alkoxy, or amino.

More preferably  $R_{22}$  is phenyl substituted, preferably mono- or disubstituted, by halogen or a halogen-containing group, e.g. 4-fluorophen-1-yl, or 3-CF<sub>3</sub>, 3-Cl, or 3,4-difluoro substituted phenyl.

More preferably  $R_{23}$  is H, halogen,  $C_1$ - $C_6$ alkyl, vinyl, phenyl, pyridyl, pyrimidyl, benzofuryl, furyl, thieryl, morpholinyl, piperidinyl, nortropanyl, piperazinyl, methyleneaminoguanidinyl or N-mono- or di- $C_1$ - $C_4$ alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by, halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, optionally mono- or di-N- $C_1$ - $C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom.

Preferably X is -NH-Y'-, -O- or -S-, where Y' is -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)- or a direct bond. In particular X is -NH-CH(CH<sub>3</sub>)-.

Thus in preferred embodiments the invention provides a compound of formula III'



wherein

R'<sub>25</sub> is phenyl or C<sub>3</sub>-C<sub>7</sub>cycloalkyl each of which is optionally mono-substituted by halogen,

C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>10</sub>alkoxy, hydroxy, trihalomethyl or -NR<sub>7</sub>R<sub>8</sub>, where R<sub>7</sub> and R<sub>8</sub> are

independently H, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>6</sub>-C<sub>10</sub>aryl, C<sub>6</sub>-C<sub>10</sub>heteroaryl, C<sub>7</sub>-C<sub>11</sub>aralkyl or C<sub>7</sub>-

C<sub>11</sub>heteroaralkyl;

R<sub>10</sub> is halogen, CF<sub>3</sub>, cyano, amido, thioamido, amino or C<sub>1</sub>-C<sub>6</sub>alkyl;

R'<sub>23</sub> is H, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, vinyl, phenyl, pyridyl, pyrimidyl, benzofuryl, furyl, thieryl, morpholinyl, piperidinyl, nortropanyl, piperazinyl, methyleneaminoguanidinyl or N-mono- or di-C<sub>1</sub>-C<sub>4</sub>alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, and

W' is -NH-Y'-, -O- or -S-, where Y' is -CH<sub>2</sub>- , -CH<sub>2</sub>-CH<sub>2</sub>- , -CH(CH<sub>3</sub>)- or a direct bond,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably R'<sub>25</sub> is unsubstituted or monosubstituted by halogen, C<sub>1</sub>-C<sub>4</sub>alkyl (e.g. methyl), C<sub>1</sub>-C<sub>4</sub>alkoxy (e.g. methoxy), hydroxy or CF<sub>3</sub>.

Preferably R'<sub>23</sub> is halogen, vinyl, phenyl, pyridyl, pyrimidyl, benzofuryl, furyl, thieryl, piperidinyl, nortropanyl, or methyleneaminoguanidinyl, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted

carbonyl, optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocycl containing from 5 to 7 ring atoms and optionally containing a further hetero atom

Preferably R<sub>10</sub> is halogen, e.g. F, or CF<sub>3</sub>.

Preferably ' is -NH-Y''' where Y''' is -CH(CH<sub>3</sub>)- or a direct bond.

The Invention includes the following compounds of formula III:

3-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole;  
4-Bromo-2-(4-fluoromethylphenyl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole;  
4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole;  
4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole;  
2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-vinylimidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(4-pyridyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-pyridyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(3-pyridyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-thienyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-furyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-amino)pyrimidylimidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-hydroxy)pyrimidylimidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-N-morpholinyl)pyrimidylimidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-thienyl)-imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(2-benzofuryl)imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(5-chlorothiophen-2-yl)imidazole;  
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-methoxyphenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-fluorophenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chloro-4-fluorophenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chloro-phenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-methyleneaminoguanidinyl-imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-ethoxycarbonyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-formyl)-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-methyl)-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy-4-tert.butyloxycarbonyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-N-tert.butyloxycarbonylnortropan-3b-yl) imidazole;

2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole;

2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole;

2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole;

2-(4-Fluorophenyl)-1-(2-cyclopentyl)amino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-nortropan-3b-yl) imidazole, and

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-acetyl)piperidine-1-yl imidazole.

It will be appreciated that when Y is substituted alkylene the compounds of formulae II and III contain at least 1 assymetric carbon atom within this alkylene moiety. The resulting diastereoisomers and enantiomers are encompassed by the instant invention. Preferably, however, e.g. for pharmaceutical use in accordance with the invention, the compounds of formulae II and III, are provided in pure or substantially pure epimeric form, e.g. as compositions in which the compounds are present in a form comprising at least 90%, e.g. preferably at least 95% of a single epimer (i.e. comprising less than 10%, e.g. preferably less than 5% of other epimeric forms). Preferred epimeric compounds of formulae II and III are described hereinafter in the Examples.

In the present description the terms such as "C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>4</sub>-C<sub>19</sub>heteroaralkyl and C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g.N, O or S, and which in the case of C<sub>4</sub>-C<sub>19</sub>heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom. Also in the present description the term "heteroaryl" includes unsaturated cyclic moieties containing heteroatoms, including furyl, benzofuryl, thienyl and the like.

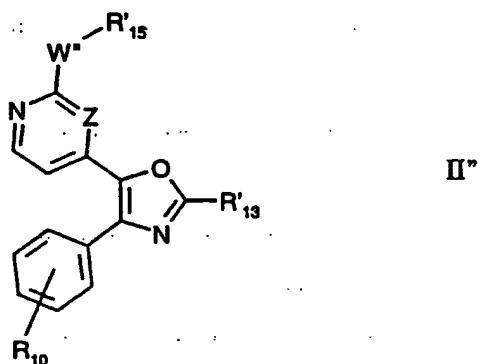
The novel oxazoles and imidazoles of the invention, in particular the compounds of formulae II, II', III and III' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of esters, e.g. pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally

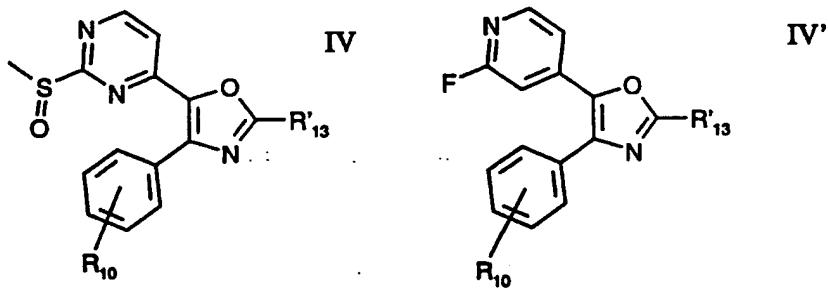
substituted lower alkanoic acid or an arylcarboxylic acid.

Agents of the Invention may also exist in the form of salts, e.g. pharmaceutically acceptable salts, and as such are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

#### Agents of the Invention of formula II'

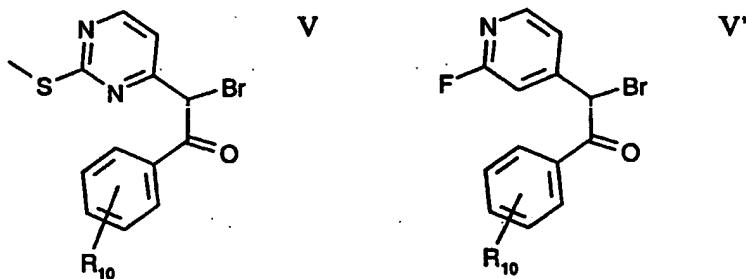


wherein R'13, R'15, R'10 and Z are as previously defined and W' is -NH-, may be prepared by reacting the corresponding precursor compound of formula IV or IV'



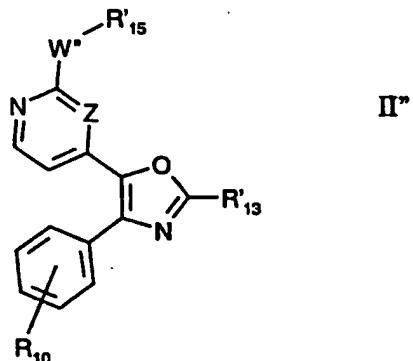
wherein R'<sub>13</sub> and R<sub>10</sub> are as previously defined, with the corresponding R'<sub>15</sub>-NH<sub>2</sub> derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane. Thereafter, if desired, the compound of Formula II' obtained may be converted into a further compound of Formula II" or otherwise treated as required.

The precursor compound of formula IV may be prepared by controlled oxidation of the corresponding 5(2-methylthio-4-pyrimidyl)-4-phenylimidazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(-4-pyrimidyl/pyridyl)-4-phenyloxazole compound may be prepared by contacting the corresponding acetophenone precursor compound of formula V or V'

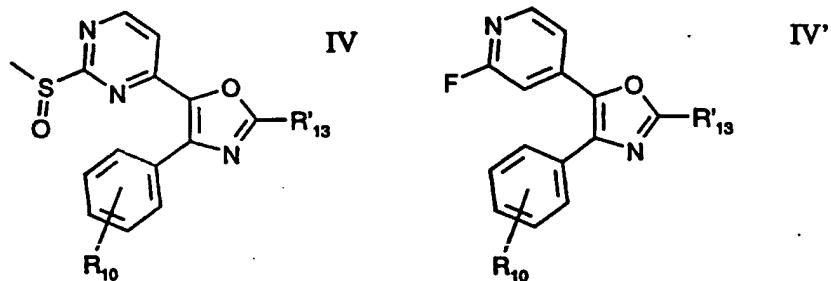


wherein R<sub>10</sub> is as defined above, with a corresponding amide of formula R'<sub>13</sub>C(O)NH<sub>2</sub>, typically at elevated temperature. The compounds of formula V and V' may be prepared by bromination of the corresponding acetophenone, e.g. 2-(2-methylthio-4-pyrimidyl)acetophenone. The acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with the corresponding pyrimidine, e.g. 4-methyl-2-(methylthio) pyrimidine, for instance in a THF containing organic solvent with cooling.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula II"

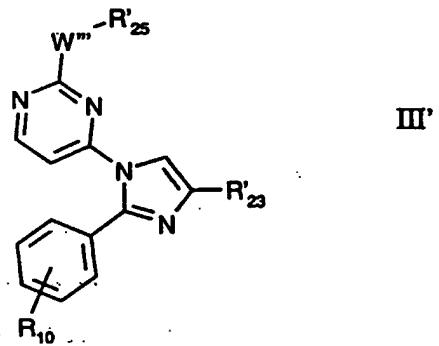


wherein R'<sub>13</sub>, R'<sub>15</sub>, R<sub>10</sub> and Z are as previously defined and W' is -NH-, which comprises reacting the corresponding precursor compound of formula IV or IV'



wherein R'<sub>13</sub>, R<sub>10</sub> and Z are as previously defined, with the corresponding R'<sub>15</sub>-NH<sub>2</sub> amine, and thereafter, if desired, converting the compound of formula II' obtained into a further compound of formula II'' or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

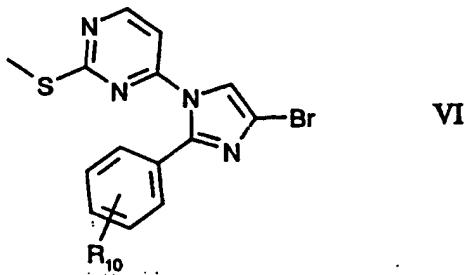
#### Agents of the Invention of formula III''



wherein R'<sub>23</sub>, R'<sub>25</sub> and R<sub>10</sub> are as previously defined and W'' is -NH- or -O-, may be prepared by reacting the corresponding compound of formula I'' in which R'<sub>23</sub> is halogen, e.g. Br, with the corresponding R'<sub>23</sub> ketone or activated R'<sub>23</sub> precursor, e.g. tri-alkylstannyl activated R'<sub>23</sub> precursor. For example, the reaction may be carried out, e.g. in the presence of a reducing agent,

such as BuLi or PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, by refluxing the reactants, and/or with cooling, in an organic solvent, as appropriate. Thereafter, if desired, the compound of Formula III' obtained may be converted into a further compound of Formula III" or otherwise treated as required.

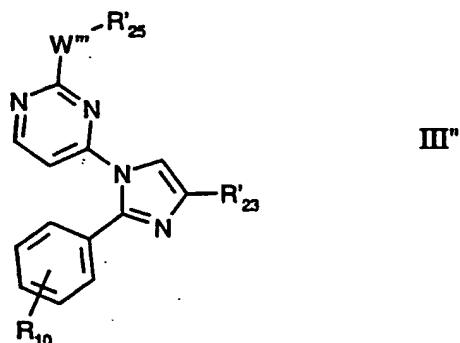
The compound of formula III" in which R'<sub>25</sub> is halogen, e.g. Br, may be prepared reacting the corresponding precursor compound of formula VI



wherein R<sub>10</sub> is as previously defined, with the corresponding R'<sub>25</sub>-NH<sub>2</sub> or R'<sub>25</sub>-OH derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane.

The corresponding 1(2-methylthio-4-pyrimidyl)-2-phenyl-4-bromo-imidazole compound may be prepared by reacting the corresponding 2-phenyl-4-bromo-imidazole compound with 4-chloro-2-methylthiopyrimidine, e.g. in the presence of KN(TMS)<sub>2</sub> in an organic solvent such as DMF. The 2-phenyl-4-bromo-imidazole compound may be obtained by removal of the trimethylsilyl-ethoxymethyl from the corresponding 1-trimethylsilyl-ethoxymethyl-2-phenyl-4-bromo-imidazole compound, which in turn may be prepared from 4,5-dibromo compound, which in turn may be prepared by phenylation of the known compound, 2,4,5-tribromo-1-(2-trimethylsilyl-ethoxymethyl)imidazole (Tetrahedron Letters (1998), 39(29), 5171-5174); for instance as hereinafter described in the Examples.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula III"



wherein R'<sub>23</sub>, R'<sub>25</sub> and R<sub>10</sub> are as previously defined and W''' is -NH- or -O-, comprising reacting a corresponding compound of formula III'' in which R'<sub>23</sub> is halogen, e.g. Br, with the corresponding R'<sub>23</sub> ketone or activated R'<sub>23</sub> precursor, e.g. tri-alkylstannyll activated R'<sub>23</sub> precursor, and thereafter, if desired, converting the compound of formula I'' obtained into a further compound of formula III'' or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

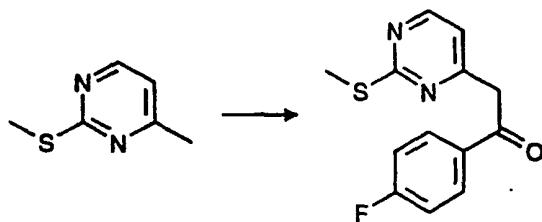
Alternative processes for preparation of Agents of the Invention are described in the Examples and are included within the scope of the present invention.

The synthesis of Agents of the Invention is further described in the following Examples.

EXAMPLES

**Example 1: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-morpholinylloxazole**

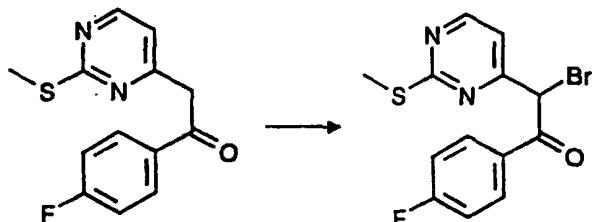
a) 4-Fluoro-2-(2-methylthio-4-pyrimidyl)acetophenone



n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78 C. 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/hexane.

1H-NMR (200 MHz CDCl<sub>3</sub>): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, 1H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomerism, signals may be duplicated.

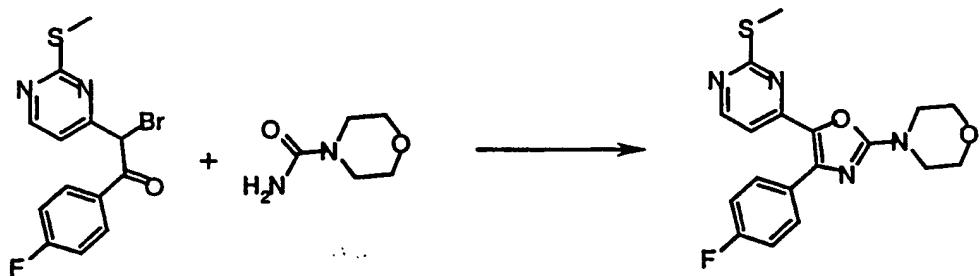
b) 4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidyl)acetophenone



Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The

residue is taken up in a saturated solution of NaHCO<sub>3</sub> and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

**c) 4-(4-Fluorophenyl)-5-([2-methylthio]-4-pyrimidyl)-2-N-morpholinylloxazole**

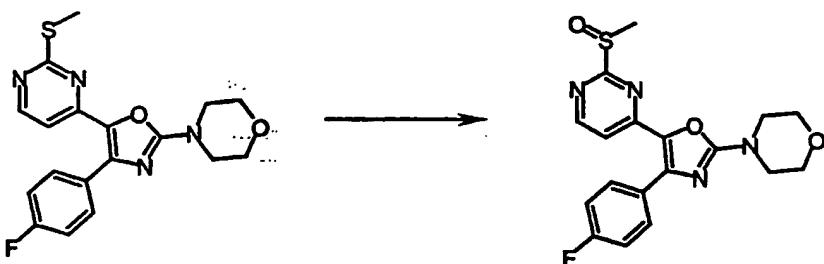


4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidyl)acetophenone (682 mg; 2 mmol) and morpholine-4-carboxylic acid amide (J. Org. Chem. 1987, 52, 3426.) (3.9 g; 30 mmol) are mixed and heated at 150 °C as a melt for 4-min. The reaction mixture is partitioned between methylene chloride and 2N Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer is extracted twice with methylene chloride. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a solid, which is purified by recrystallisation from acetone/hexane to yield the title compound as colorless crystals (140 mg; 19%).

1H-NMR (400MHz; CDCl<sub>3</sub>): 3.60 (dd, 4H); 3.78 (dd, 4H); 6.92 (d, 1H); 7.02 (dd, 2H); 7.90 (dd, 2H); 8.32 (d, 1H).

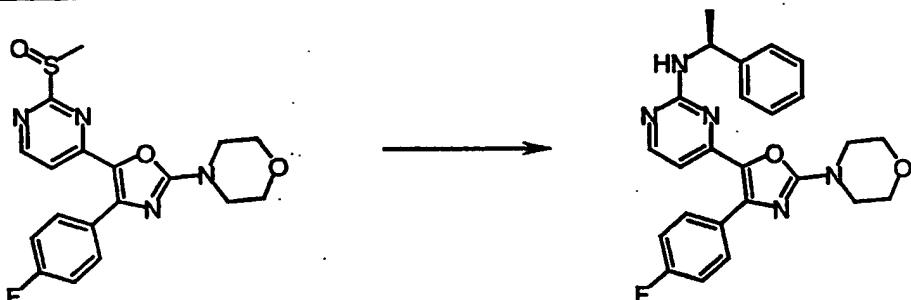
MS (m/z) EI: 372 (M+, 100).

**d) 4-(4-Fluorophenyl)-5-([2-methylsulfinyl]-4-pyrimidyl)-2-N-morpholinylloxazole**



4-(4-Fluorophenyl)-5-([2-methylthio]-4-pyrimidyl)-2-N-morpholinylloxazole (135 mg; 0.365 mmol) is dissolved in methylene chloride, cooled to 0 C and treated with mCPBA (100 mg; 0.49 mmol) for 15 min. The reaction mixture is poured on saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with ethyl acetate three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness yielding the title compound as a yellow foam (140 mg; 95%) which is used for the next step without further purification.

**e) 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-morpholinylloxazole**



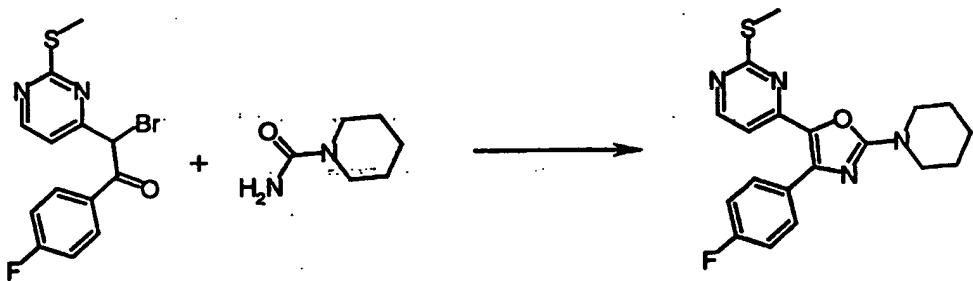
4-(4-Fluorophenyl)-5-([2-methylsulfinyl]-4-pyrimidyl)-2-N-morpholinylloxazole (140 mg; 0.36 mmol) and 1-(S)-phenylethylamine (0.7 ml) are heated at 120 C for 2h. After evaporation of the amine, the product is purified by preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min the title product as colorless foam (75 mg; 44%).

1H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.41 (bd, 3H); 3.50-3.60 (bs, 4H); 3.68-3.76 (bs, 4H); 4.81-5.10 (bs, 1H); 6.71 (d, 1H); 7.00-7.30 (m, 7H); 7.58 (bs, 1H, NH); 7.93-8.16 (bs, 2H); 8.23 (d, 1H).

MS (m/z) EI: 445 (M+, 100); 430 (50); 359 (10).

**Example 2: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-piperidinyloxazole**

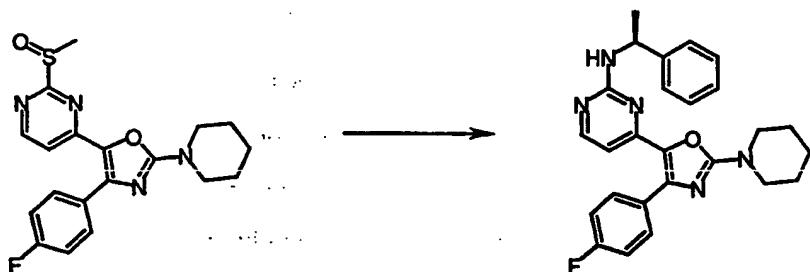
**a) 4-(4-Fluorophenyl)-5-([2-methylthio]-4-pyrimidyl)-2-N-piperidinyloxazole**



4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidyl)acetophenone (682 mg; 2 mmol) and piperidine-N-carboxylic acid amide (Pharmazie 1989, 44, 225.) (3.9 g; 30 mmol) are mixed and heated at 155 C as a melt for 5 min. The reaction mixture is partitioned between methylene chloride and 2N Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer is extracted twice with methylene chloride. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a solid, which is purified by recrystallisation from TBME to yield the title compound as colorless crystals (210 mg; 28%).

MS (m/z) EI: 370 (M+, 100).

**b) 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-piperidinyloxazole**

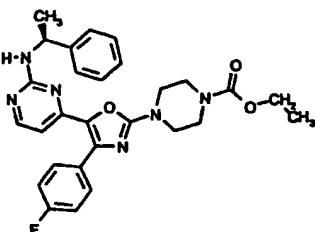
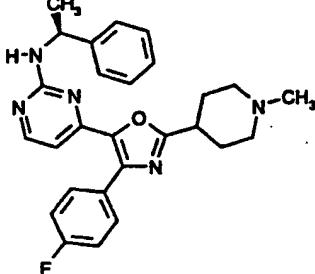
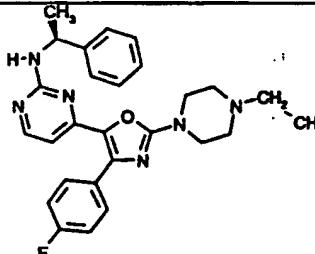


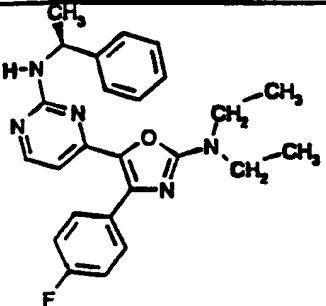
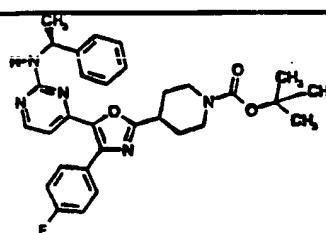
4-(4-Fluorophenyl)-5-((2-methylsulfonyl)-4-pyrimidyl)-2-N-piperidinyloxazole (prepared in analogy to intermediate 1b) (220 mg; 0.566 mmol) and 1-(S)-phenylethylamine (0.9 ml) are heated at 120 C for 1 h. After evaporation of the amine, the product is purified by SiO<sub>2</sub> chromatography (acetone/cyclohexylamine 5/95) to yield the title compound as yellow crystals (135 mg; 56%).

1H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.41 (d, 3H); 1.60 (s, 6H); 3.55 (s, 4H); 4.83-5.05 (bs, 1H); 6.65 (d, 1H); 7.03-7.31 (m, 7H); 7.53 (bs, 1H, NH); 7.92-8.15 (bs, 2H); 8.23 (d, 1H).

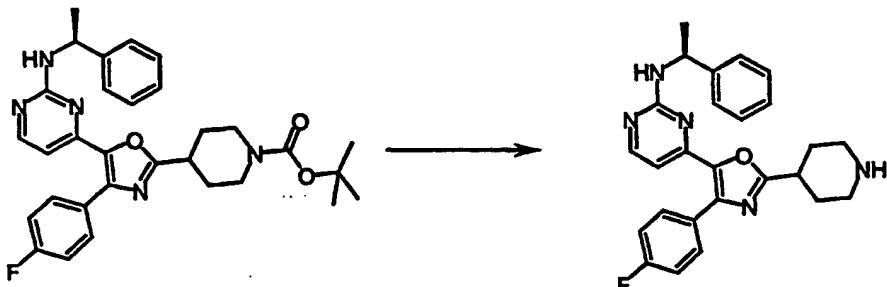
MS (m/z) EI: 443 (M+); 428 (40).

The following compounds of Examples 3 to 7 are prepared analogously to the compounds of Examples 1 and 2:

| Example | Compound  | NMR   | MS  |
|---------|---|---|---|
| 3       |    | 1H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.21 (t, 3H); 1.41 (bd, 3H); 3.55 (bd, 4H); 3.60 (bd, 4H); 4.09 (q, 2H); 4.82-5.05 (bs, 1H); 6.70 (d, 1H); 7.02-7.31 (m, 7H); 7.58 (bs, 1H, NH); 7.93-8.15 (bs, 2H); 8.37 (d, 1H).       | MS (e/z) EI: 457 (M+, 60); 442 (10); 401 (10); 387 (100); 105 (20).                     |
| 4       |   | 1H-NMR (400MHz; DMSO-d6, 120 C): 1.47 (d, 3H); 1.82-1.96 (m, 2H); 2.01-2.20 (m, 4H); 2.25 (s, 3H); 2.75-2.95 (m, 3H); 5.02-5.11 (m, 1H); 6.81 (d, 1H); 7.06 (s, 1H, NH); 7.18 (dd, 2H); 7.23-7.30 (m, 5H); 8.02 (dd, 2H); 8.32 (d, 1H). | MS (e/z) EI: 457 (M+, 60); 442 (10); 401 (10); 387 (100); 105 (20).                     |
| 5       |  | 1H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.05 (t, 3H); 1.42 (bd, 3H); 2.40 (q, 4H); 2.49 (bt, 4H); 3.58 (bt, 4H); 4.82-5.07 (bs, 1H).   | MS (e/z) EI: 472 (M+, 95); 457 (25); 401 (30); 388 (100); 375 (60); 360 (30); 105 (60). |

|   |  |  |   |
|---|--|--|---|
|   |  | 1H); 6.70 (d, 1H); 6.90-7.42 (m, 7H); 7.90-8.10 (m, 3H); 8.73 (d, 1H).   |   |
| 6 |   | 1H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.20 (t, 6H); 1.42 (d, 3H); 3.53 (q, 4H); 4.83-5.03 (bs, 1H); 6.65 (d, 1H); 7.05-7.45 (m, 7H); 7.53 (bs, 1H); 7.92-8.13 (m, 2H); 8.23 (d, 1H)                         | MS (e/z) EI: 431 (M+, 100); 416 (50); 359 (10); 120 (50); 105 (40) 95 (20). |
| 7 |  | 1H-NMR (400MHz; CDCl3): 1.43 (s, 9H); 1.53 (bs, 3H); 1.80 (bq, 2H); 2.05 (bd, 2H); 2.82-3.05 (m, 3H); 4.00-4.16 (m, 2H); 5.00 (bs, 1H); 6.71 (d, 1H); 6.98 (bt, 2H); 7.11-7.28 (m, 5H); 7.83 (dd, 2H); 8.21 (d, 1H). | MS (e/z) EI: 543 (M+, 30); 442 (50); 387 (90); 105 (60).                    |

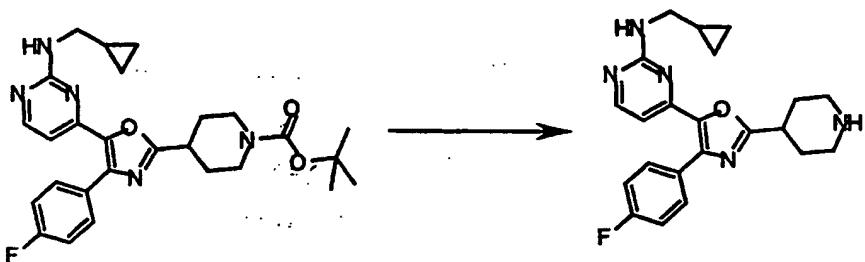
Example 8: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole



4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-tert.butyloxycarbonylpiperidine-1-yl)oxazole (650 mg; 1.19 mmol, the product of Example 7 above) is stirred in EtOH/HCl conc (1:1; 24 ml) for 30 min, then poured on a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a solid, which is purified by recrystallisation from TBME to yield the HCl-salt of the title compound as colorless crystals (180 mg; 33%)

1H-NMR (400MHz; DMSO-d6) of HCl salt; mixture of rotamers: 1.42 (bs, 3H); 1.93-2.08 (m, 2H); 2.19-2.31 (m, 2H); 2.98-3.11 (m, 2H); 3.28-3.48 (m, 3H); 4.75-5.25 (bs, 1H); 6.82 (bs, 1H); 6.98-7.43 (m, 7H); 7.82 (d, 1H); 7.90-8.22 (m, 2H); 8.38 (bs, 1H); 8.95 (bs, 2H, NH2)  
MS (e/z) EI: 443 (M+); 387 (80); 105 (100).

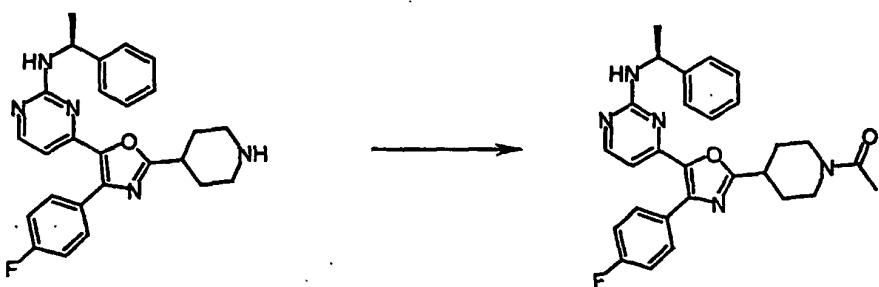
Example 9: 4-(4-Fluorophenyl)-5-(2-cyclopropylmethyamino-4-pyrimidyl)-2-(4-NH-piperidin-1-yl)oxazole



4-(4-Fluorophenyl)-5-(2-cyclopropylmethyamino-4-pyrimidyl)-2-(4-tert.butyloxycarbonylpiperidine-1-yl)oxazole (prepared in analogy to example 7) (1.12g; 2.27 mmol) is dissolved at 0°C in CH<sub>2</sub>Cl<sub>2</sub>/CF<sub>3</sub>COOH (8ml; 1:1) and stirred for 10 min. at 10-15°C. The reaction mixture is poured on cold 2N NaOH; the precipitated solid is filtered and recrystallised from EtOH/Hexane to yield the title compound (775mg; 87%) as colorless crystals.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 0.20 (bs, 2H); 0.53 (bd, 2H); 1.03 (bs, 1H); 1.82-1.98 (m, 2H); 2.15 (bd, 2H); 2.80 (bt, 2H); 3.02-3.12 (m, 1H); 3.12-3.30 (m, 4H); 5.24 (bs, 1H, NH); 6.86 (d, 1H); 7.12 (t, 2H); 8.05 (bs, 2H); 8.32 (d, 1H).  
 MS (e/z) Cm/ES-: 392.1 (M-H, 100). MS (e/z) Cm/ES+: 394.0 (MH+, 100).

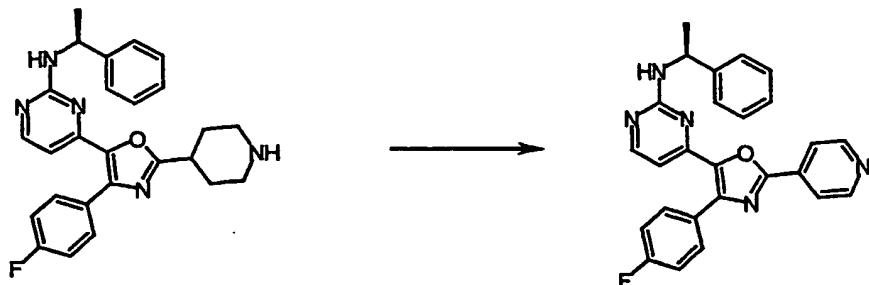
**Example 10: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-N-acetyl-piperidine-1-yl)oxazole**



4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole (44.4 mg; 0.1 mmol) is dissolved in THF/pyridine (1.0 ml/0.5 ml) and treated with acetyl chloride (0.007 ml; 0.1 mmol) for 1 h at room temperature. The reaction mixture is evaporated and partitioned between ethyl acetate and 2 N Na<sub>2</sub>CO<sub>3</sub>. The aqueous phase is extracted three times with ethyl acetate. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a foam, which is purified by SiO<sub>2</sub> chromatography (acetone/hexane 10/90 to 25/75) to yield the title compound (40 mg; 90%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6, 120 C): 1.48 (d, 3H); 1.71-1.97 (m, 2H); 2.04 (s, 3H); 2.07-2.15 (m, 2H); 3.05-3.21 (bs, 2H); 3.21-3.30 (m, 1H); 3.95-4.15 (bs, 2H); 5.03-5.11 (m, 1H); 6.82 (d, 1H); 7.10 (d, 1H, NH); 7.18 (dd, 2H); 7.23-7.30 (m, 5H); 8.03 (dd, 2H); 8.35 (d, 1H).  
 MS (e/z) EI: 485 (M+); 470 (60); 442 (20); 387 (80); 105 (55).

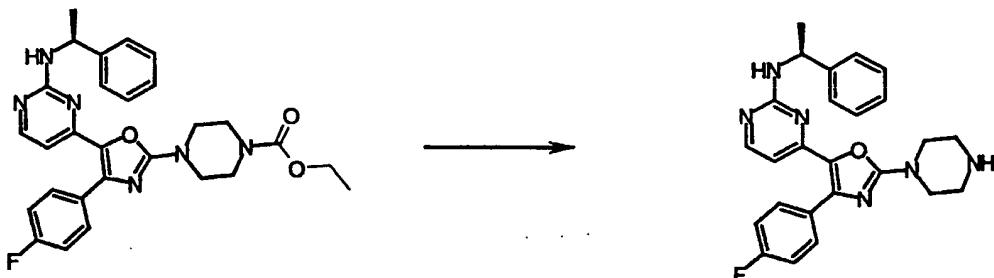
**Example 11: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-pyridyl) xazole**



4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole (44.4 mg; 0.1 mmol) is dissolved in xylenes (5 ml) and treated with 10 % Pd/C (20 mg) at 125 C while blowing air through the reaction mixture for 12 h. The mixture is filtered, evaporated to dryness and purified by SiO<sub>2</sub> chromatography (acetone/cyclohexane 20/80) to yield the title compound as a yellow foam (10 mg; 23 %).

MS (e/z) EI: 437 (M<sup>+</sup>; 50); 422 (60).

**Example 12: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-piperazinyl) oxazole**



4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-ethoxy-carbonylpiperazin-1-yl)oxazole (130 mg; 0.251 mmol) in CHCl<sub>3</sub> (2.6 ml) is treated with trimethylsilyl iodide (0.113 ml; 0.83 mmol) at 60 C. After 3 h a second portion of trimethylsilyl iodide (0.113 ml; 0.83 mmol) is added and the reaction heated at 60 C for 21 h. 6 M HCl in 1-propanol (3 ml) is added to the reaction mixture, stirred until dissolution is complete and then poured on a saturated solution of Na<sub>2</sub>CO<sub>3</sub>.

The aqueous phase is extracted three times with ethyl acetate. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a foam, which

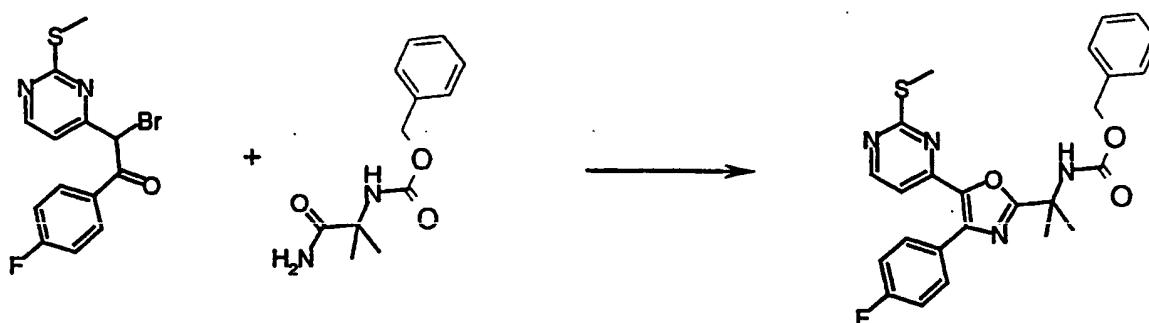
was purified by SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub> conc 90/9/1 to 85/15/1.5) to yield the title compound as a yellow foam (80 mg; 72 %).

<sup>1</sup>H-NMR (400MHz; DMSO-d6). Mixture of rotamers: 1.40 (d, 3H); 2.79-2.83 (m, 4H); 3.52 (m, 4H); 4.80-5.05 (bs, 1H); 6.67 (d, 1H); 7.03-7.33 (m, 7H); 7.53 (bs, 1H, NH); 7.91-8.15 (bs, 2H); 8.23 (d, 1H).

MS (e/z) EI: 445 (MH+, 75).

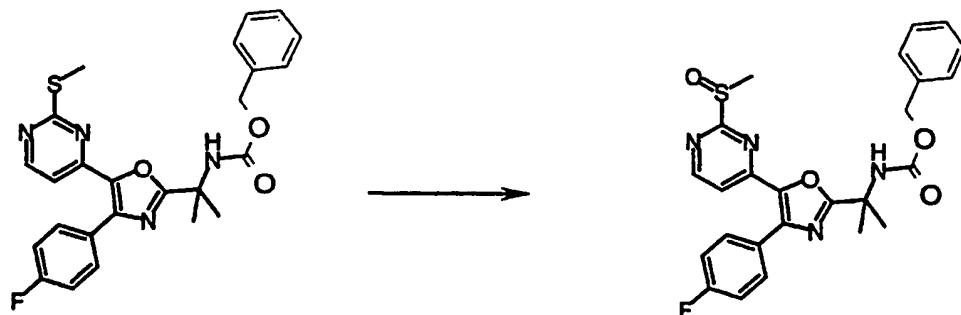
**Example 13: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-amino-1-methyl)ethyloxazole**

**a) 4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidyl)-2-(1-N-benzyloxy-carbonyl)amino-1-methyl)ethyloxazole**



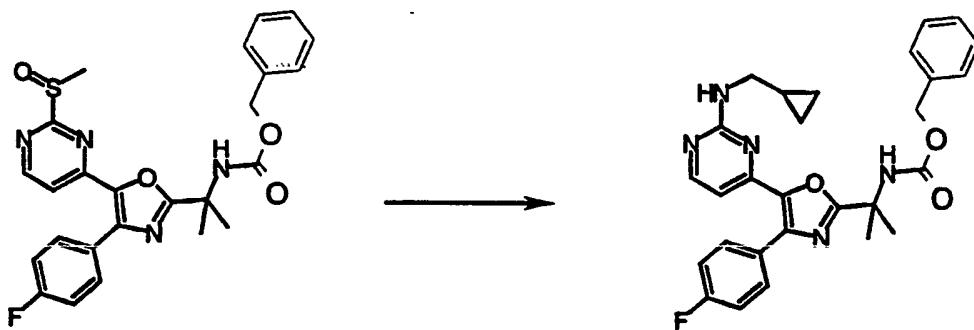
4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidyl)acetophenone (2.39 g; 7 mmol) and N-carbobenzyloxy-2-methyl-alanine amide (14 g, 41 mmol) are refluxed in xylenes (35 ml) for 7 h. The reaction mixture is evaporated and purified via SiO<sub>2</sub> chromatography (acetone/cyclohexane 10/90) to yield the title compound (900 mg; 27 %).

**b) 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidyl)-2-(1-N-benzyloxy-carbonyl)amino-1-methyl)ethyloxazole**



4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidyl)-2-(1-N-benzyloxy-carbonyl)amino-1-methyl-ethyloxazole (960 mg; 2 mmol) is dissolved in methylene chloride (20ml), cooled to 0C and treated with mCPBA (490 mg; 2 mmol 70%) for 30 min at 0 C. The reaction mixture is poured on 2 N Na<sub>2</sub>CO<sub>3</sub> and extracted with ethyl acetate 3 times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give a foam, which is used for the next step without further purification.

**c) 4-(4-Fluorophenyl)-5-(2-cyclopropylmethylamino-4-pyrimidyl)-2-(1-(N-benzyloxycarbonyl)amino-1-methyl)ethyloxazole**

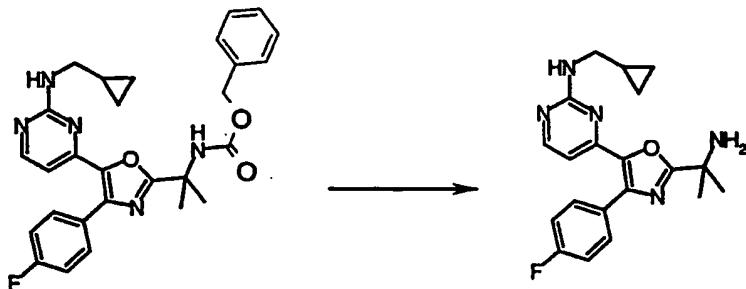


4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidyl)-2-(1-N-benzyloxy-carbonyl)amino-1-methyl-ethyloxazole (900 mg; 1.8 mmol) and cyclopropylmethylamine (2 ml) are refluxed for 1 h. The reaction mixture is evaporated and purified via SiO<sub>2</sub> chromatography (acetone/cyclohexane 10/90 to 20/80) yielding the title compound as a yellow foam (670 mg; 73%).

1H-NMR (400MHz; DMSO-d6): Mixture of rotamers: 0.03-0.18 (bs, 2H); 0.31-41 (bs, 2H); 0.87-1.01 (bs, 1H); 1.68 (s, 6H); 2.94-3.09 (m, 2H); 5.03 (s, 2H); 6.70 (d, 1H); 7.20-7.40 (m, 8H); 8.04-8.22 (bs, 3H); 8.34 (d, 1H).

MS (e/z) EI: 501 (M+, 20); 410 (20); 309 (50); 91 (100).

**d) 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-amino-1-methyl)ethyloxazole**



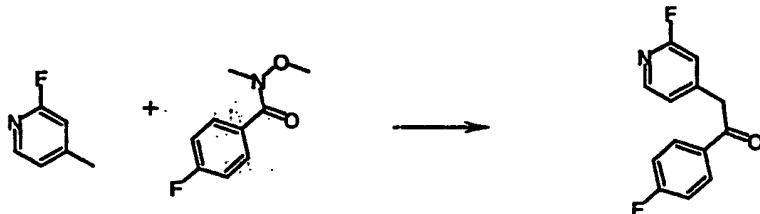
4-(4-Fluorophenyl)-5-(2-cyclopropylmethylamino-4-pyrimidyl)-2-(1-(N-benzyloxycarbonyl)amino-1-methyl)ethyloxazole (620 mg; 1.25 mmol) is dissolved in EtOH (100 ml) and hydrogenated at 1 atm over 10 % Pd/C (1.3 g). Hydrogen uptake is complete after 1 h. Pd/C is filtered off, the solvent evaporated and the resulting product purified via SiO<sub>2</sub> chromatography (ethyl acetate/EtOH/NH<sub>3</sub>, conc 95/4.5/0.5 to 80/18/2) to yield the title compound (260 mg; 57 %)

1H-NMR (400MHz; DMSO-d6): Mixture of rotamers: 0.03-0.13 (bs, 2H); 0.31-0.41 (bs, 2H); 0.86-1.03 (bs, 1H); 1.51 (s, 6H); 2.30 (bs, 2H, NH<sub>2</sub>); 3.03 (bs, 2H); 6.93 (d, 1H); 7.27 (dd, 2H); 7.33 (bt, 1H, NH); 8.08-8.16 (bs, 2H); 8.47 (d, 1H).

MS (e/z) ESI: 368.2 (MH<sup>+</sup>, 100).

**Example 14: 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-hydroxy-4-methylpiperidine-1-yl)oxazole**

**a) 4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone**



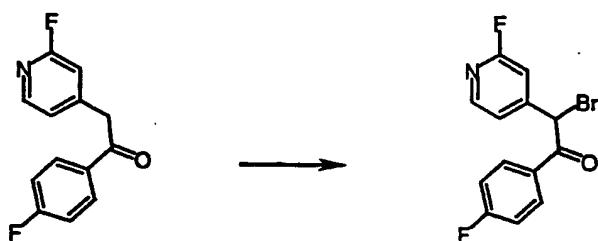
Diisopropylamine (0.93 ml; 6.55 mmol) in THF (6 ml) is cooled to -78 C and treated with nBuLi (3.8 ml; 6.08 mmol of a 1.6 M solution in hexane). 2-Fluoro-4-methylpyridine (620 mg; 5.4 mmol) is added dropwise and stirred under argon for 30 min. 4-Fluoro-N-methoxy-N-methylbenzamide (1 g; 5.46 mmol) is added dropwise in THF (0.5 ml) and the reaction mixture allowed to warm up to room temperature within 10 min. then poured on a saturated solution of

NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound as pale yellow crystals. Purification by recrystallisation from hot TBME rendered the desired compound as white solid (630 mg; 50 %).

<sup>1</sup>H-NMR (200 MHz; CDCl<sub>3</sub>): 4.35 (s, 2H); 6.88 (s, 1H); 7.08-7.30 (m, 3H); 7.99-8.15 (dd, 2H); 8.20 (d, 1H).

MS (e/z) ESI: 233 (M+, 5); 123 (100).

**b) 4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone**

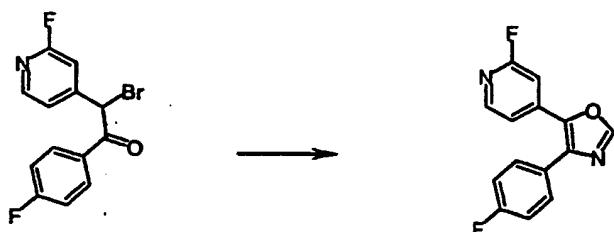


4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone (0.5 g; 2.1 mmol) dissolved in acetic acid (4 ml) is treated with bromine (0.34 g; 2.1 mmol) in acetic acid (1 ml) at room temperature for 2.5 h under stirring. The light brown solution is evaporated to dryness, dissolved in ether and extracted three times with diethyl ether. The combined organic phases are washed with a saturated solution of NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound as pale yellow oil (0.67 g; 100%).

<sup>1</sup>H-NMR (200 MHz; CDCl<sub>3</sub>): 6.15 (s, 1H); 7.10-7.38 (m, 4H); 8.08 (dd, 2H); 8.23 (d, 1H).

MS (e/z) ESI: 232 (M-Br); 204 (10); 203 (12); 123 (100).

**c) 4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)oxazole**



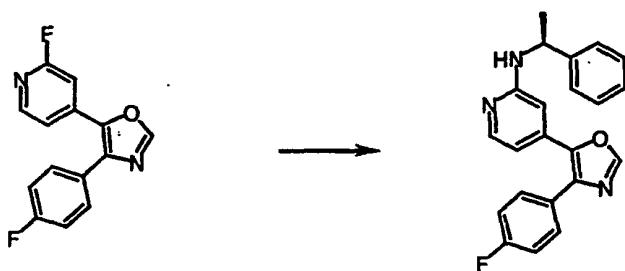
4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone (6 g; 19.23 mmol) is dissolved in formamide (100 ml), treated with H<sub>2</sub>SO<sub>4</sub>conc (60 drops) and heated to 145 C for 6 min and 125

C for 15 min. The reaction mixture is poured on 2 N Na<sub>2</sub>CO<sub>3</sub> and extracted with TBME 3 times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness and purified via SiO<sub>2</sub> chromatography (acetone/hexane 1/9) to yield the title compound as a white solid (1.92 g; 39 %).

<sup>1</sup>H-NMR (400MHz; DMSO-d6): 7.29 (s, 1H); 7.48 (t, 2H); 7.45 (d, 1H); 7.69 (dd, 2H); 8.32 (d, 1H); 8.74 (s, 1H).

MS (e/z) EI: 258 (M+, 100); 230 (20); 202 (40).

**d) : 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]aminopyridin-4-yl)oxazole**

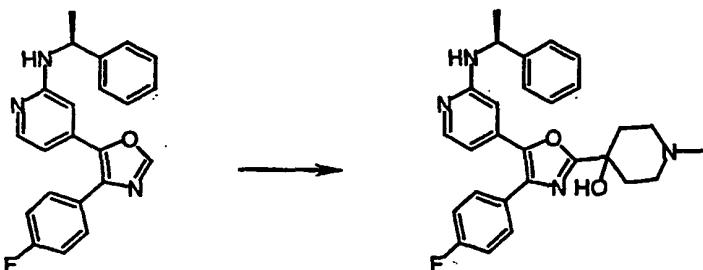


4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)oxazole (50 mg; 0.19 mmol) and S-(1)-phenylethylamine (0.5 ml) is heated to 180 C for 1.5 h, evaporated and purified via SiO<sub>2</sub> chromatography to yield the title compound as a colorless foam (34 mg; 50%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6): 1.40 (d, 3H); 4.96 (bt, 1H); 6.53 (d, 1H); 6.68 (s, 1H); 7.11-7.40 (m, 8H); 7.63 (dd, 2H); 7.95 (d, 1H); 8.06 (s, 1H).

MS (e/z) EI: 359 (M+, 100); 344 (90); 272 (40); 120 (40); 105 (50).

**e) 4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-hydroxy-4-methylpiperidine-1-yl)oxazole**



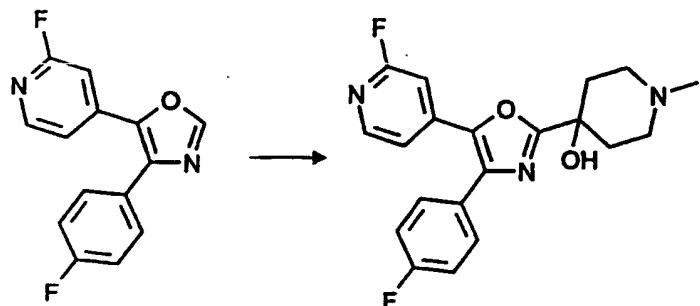
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]aminopyridin-4-yl)oxazole (100 mg; 0.278 mmol) is dissolved in THF (1.4 ml) and cooled to -40 C. nBuLi (0.48 ml; 0.8 mmol of a 1.6 M solution in hexane) is added at -40 C dropwise while stirring under argon. After 10 min N-methyl-4-

piperidone (0.09 ml; 0.75 mmol) is added and stirring continued for 10 min. The reaction mixture is poured on a saturated solution of NaCl and extracted with TBME 3 times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness and purified via SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub>conc 100/0/0 to 80/20/1) to yield the title compound as a slightly yellow foam (26 mg; 20%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6) mixture of rotamers: 1.20-1.33 (m, 2H); 1.40 (d, 3H); 1.97-1.98 (bd, 2H); 2.12 (s, 0.9H); 2.17 (s, 2.1 H); 2.30-2.53 (m, 4H); 4.91-5.03 (m, 1H); 5.67 (s, 1H, OH); 6.50 (d, 1H); 6.69 (s, 1H); 7.10-7.42 (m, 8H); 7.61 (dd, 2H); 7.93 (d, 1H).  
MS (e/z) EI: 472 (M+, 25); 454 (20; 71 (100).

**Example 15: 4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-pyridyl)oxazole**

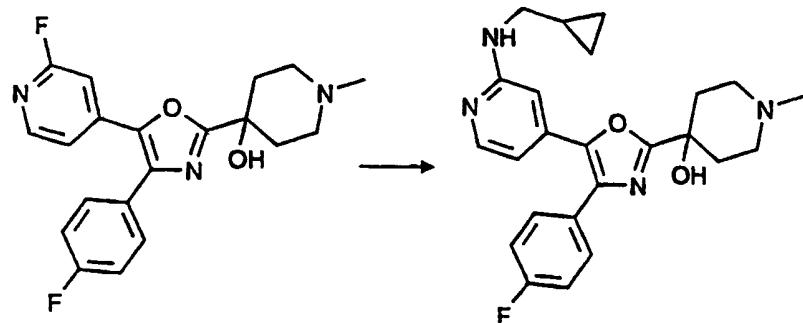
**a) 4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole**



4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)oxazole (100 mg; 0.38 mmol) is dissolved in THF (1.4 ml), cooled under argon and stirring to -40 C and treated with nBuLi (0.242 ml; 0.387 mmol of a 1.6 M solution in hexane) for 5 min. N-methyl-4-piperidone is then added and the reaction stirred for another 5 min at -40 C, poured on a saturated solution of NaCl and extracted with TBME 3 times. The combined organic phases are washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness and purified via SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub>conc 95/5/0.5 to 90/10/1) to yield the title compound as colorless crystals (95 mg; 67%).

MS (e/z) EI: 371 (M+, 20); 354 (10), 301 (20).

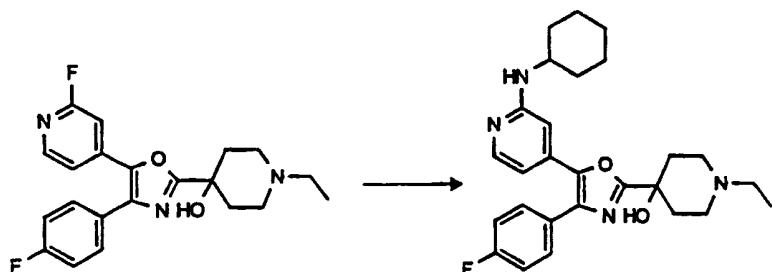
**b) 4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-[cyclopropyl]-methyl]amino-4-pyridyl)oxazole**



4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole (90 mg; 0.245 mmol) and (aminomethyl)cyclopropane (4 ml) are heated in a sealed steel cylinder at 190 C for 1.5 h, the amine evaporated and the residue purified via SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub>conc 90/10/1) to yield the title compound (61 mg; 60%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6): 0.17 (bq, 2H); 0.43 (bq, 2H); 0.95-1.05 (m, 1H); 1.88-1.98 (bd, 2H); 2.07-2.18 (m, 2H); 2.19 (s, 3H); 2.46-2.50 (bs, 4H); 3.08-3.12 (m, 2H); 5.68 (s, 1H, OH); 6.51 (d, 1H); 6.68 (s, 1H); 6.87 (t, 1H, NH); 7.32 (t, 2H); 7.65 (dd, 2H); 7.97 (d, 1H).  
MS (e/z) EI: 422 (M+, 30); 404 (30); 352 (30); 71 (100)

**Example 16: 4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole**

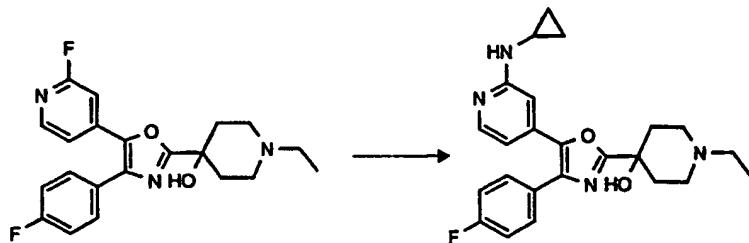


The title compound is prepared according to the procedure above and obtained as colorless crystals in 83% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 1.16 (t, 3H); 1.16-1.40 (m, 6H); 1.61-1.81 (m, 2H); 1.92-2.06 (m, 4H); 2.40 (dt, 2H); 2.48-2.61 (m, 4H); 2.78 (bd, 2H); 2.92 (s, 1H, OH); 3.36 (m, 1H); 4.53 (d, 1H, NH); 6.45 (s, 1H); 6.67 (d, 1H); 7.13 (t, 2H); 7.63 (dd, 2H); 8.08 (d, 1H).

MS (e/z) EI: 464 (M+, 60); 447 (50); 446 (55).

**Example 17: 4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidine-1-yl)-5-(2-cyclopropylamino-4-pyridyl)oxazole**



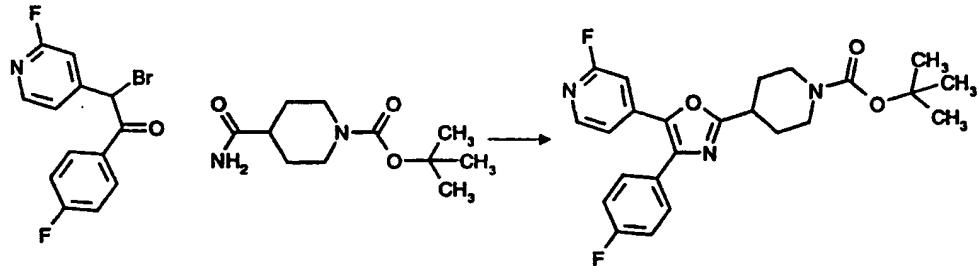
The title compound is prepared according to the procedure above and obtained as cream colored crystals in 48% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 0.48 (m, 2H); 0.66 (m, 2H); 1.13 (t, 3H); 2.02 (bd, 2H); 2.34-2.46 (m, 3H); 2.49-2.62 (m, 4H); 2.78 (bd, 2H); 3.06 (s, 1H, OH); 5.17 (s, 1H, NH); 6.79 (dd, 1H); 6.87 (s, 1H); 7.13 (t, 2H); 7.68 (dd, 2H); 8.08 (d, 1H).

MS (e/z) EI: 422 (M+, 50); 405 (28); 404 (30); 338 (28); 85 (100).

**Example 18: 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole**

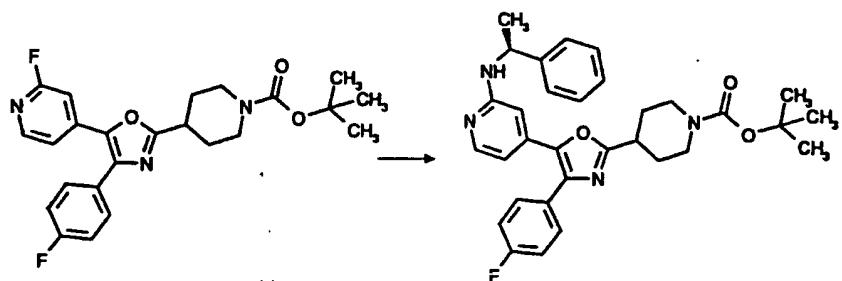
**a) 4-(4-Fluorophenyl)-2-(4-N-tert.butyloxycarbonyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole**



4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone (2.1 g; 4.76 mmol) and 1-tert.butyloxycarbonyl piperidine-4-carboxylic acid amide (6 g; 26.3 mmol) are mixed and heated as a melt at 162 C for 20 min. The reaction mixture is dissolved in MeOH (ca 10 ml) and combined with TBME (130 ml). The precipitate is filtered off, the filtrate evaporated to dryness and treated with EtOH/HClconc (2 ml/2 ml) for 10 min, poured on water and extracted three times with TBME. The aqueous phase is adjusted to pH ~10 by adding a saturated solution of

$\text{Na}_2\text{CO}_3$  and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness and yielded the piperidine NH analogue of the title compound (177 mg; 0.52 mmol; 8%), which is treated with  $(\text{BOC})_2\text{O}$  (150 mg; 0.68 mmol) in THF (2 ml) for 1 h at room temperature. The reaction mixture is evaporated to yield the title compound as a colorless foam (270 mg), which is directly used for the next step without purification.

**b) 4-(4-Fluorophenyl)-2-(4-N-tert.butyloxycarbonyl)piperidine-1-yl)-5-[2-(1-(S)-phenylethyl)amino-4-pyridyl]oxazole**

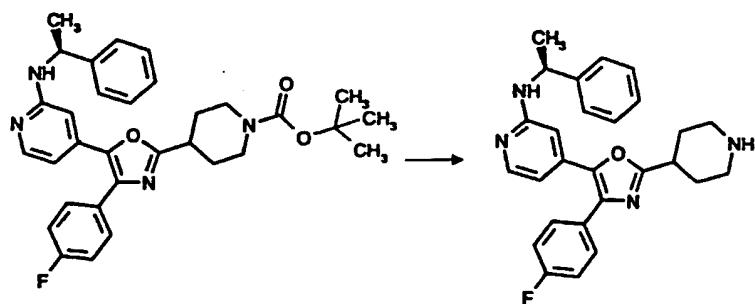


4-(4-Fluorophenyl)-2-(4-N-tert.butyloxycarbonyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole (270 mg) and 1-(S)-phenylethylamine (3 ml) are heated to 185 C for 2.5 h, evaporated and purified by  $\text{SiO}_2$  chromatography (TBME/hexanes 1/1 to 100/0) to yield the title compound as a colorless foam (145 mg; 52%).

$^1\text{H-NMR}$  (400MHz; DMSO-d6) mixture of rotamers: 1.40-1.45 (s, 12H); 1.56-1.71 (m, 2H); 2.00-2.08 (bd, 2H); 2.90-3.05 (bs, 2H); 3.08-3.19 (m, 1H); 3.90-4.02 (bd, 2H); 4.90-5.00 (bs, 1H); 6.49 (d, 1H); 6.66 (s, 1H); 7.13-7.32 (m, 8H); 7.60 (dd, 2H); 7.91 (d, 1H).

MS (e/z) EI: 542 (M+, 100); 485 (30); 441 (30); 386 (60); 120 (60); 105 (60); 57 (75).

**c) 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole**



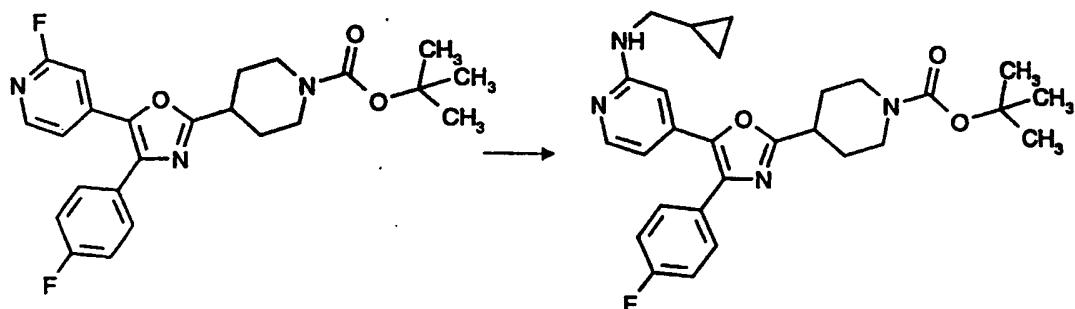
4-(4-Fluorophenyl)-2-(4-N-tert.butyloxy carbonyl)piperidine-1-yl)-5-[2-(1-(S)-phenylethyl]amino-4-pyridyl)oxazole (140 mg; 0.258 mmol) is dissolved in EtOH/HCl conc (4 ml; 1:1) and treated at room temperature for 5 min. Water is added and the reaction mixture extracted with TBME twice. The combined organic phases are mixed with a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with ethyl acetate three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield the title compound as a colorless foam (90 mg; 80%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6) mixture of rotamers: 1.42 (d, 3H); 1.58-1.70 (m, 2H); 1.92-2.03 (m, 2H); 2.08-2.30 (bs, 1H, NH); 2.55-2.65 (dd, 2H); 2.92-3.03 (m, 3H); 4.90-5.00 (m, 1H); 6.48 (d, 1H); 6.66 (s, 1H); 7.15-7.33 (m, 8H); 7.58 (dd, 2H); 7.90 (d, 1H).

MS (e/z) EI: 442 (M+, 70); 386 (100); 105 (55).

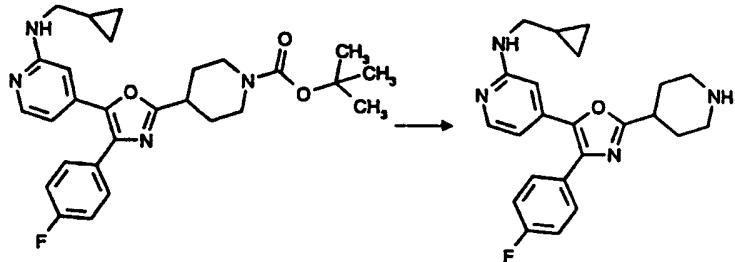
**Example 19: 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole**

a) **4-(4-Fluorophenyl)-2-(4-N-tert.butyloxy carbonyl)piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole**



4-(4-Fluorophenyl)-2-(4-N-tert.butyloxy carbonyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole (200 mg; 0.45 mmol) and (aminomethyl)cyclopropane (2 ml) are refluxed for 3.5 h, evaporated and purified by SiO<sub>2</sub> chromatography (TBME/hexanes 4/6) to yield the title compound as a colorless foam (190 mg; 85%).

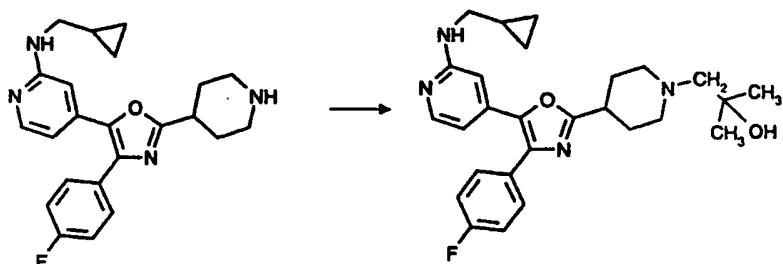
**b) 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole**



is treated with EtOH/HCl conc in analogously as for compound 14.

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): 0.19 (dd, 2H); 0.45 (dd, 2H); 0.95-1.06 (m, 1H); 1.58-1.71 (dq, 2H); 1.92-2.01 (dd, 2H); 2.08-2.28 (bs, 1H, NH); 2.61 (dt, 2H); 2.93-3.03 (m, 3H); 3.10 (t, 2H); 6.50 (d, 1H); 6.67 (s, 1H); 6.82 (t, 1H, NH); 7.30 (t, 2H); 7.65 (dd, 2H); 7.97 (d, 1H).  
MS (e/z) ESI: 393.2 (MH<sup>+</sup>, 60).

**Example 20: 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole**



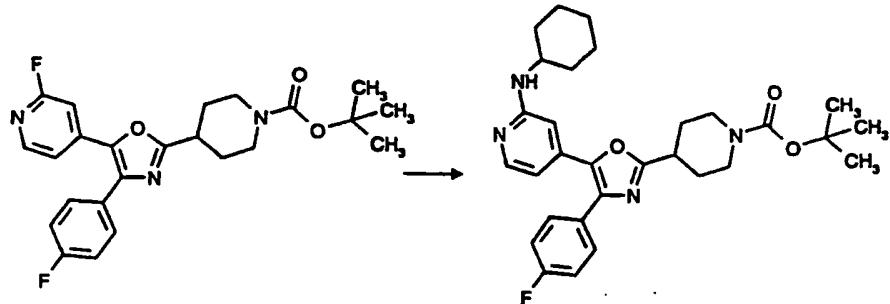
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-[cyclopropylmethyl]amino-4-pyridyl)oxazole (76 mg; 0.19 mmol) and isobutylene oxide (0.1 ml; 1.4 mmol) are dissolved in ethanol and heated in a closed vessel to 80 C for 2 h. Evaporation to dryness and purification via SiO<sub>2</sub> chromatography rendered the title compound as a white solid (51 mg; 57%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): 0.18 (dd, 2H); 0.44 (dq, 2H); 0.93-1.05 (m, 1H); 1.11 (s, 6H); 1.84 (dq, 2H); 1.99 (bd, 2H); 2.21 (s, 2H); 2.28 (bt, 1 H); 2.82-2.91 (m, 1H); 2.97 (bd, 2H); 3.10 (t, 2H); 4.07 (s, 1H, OH); 6.49 (d, 1H); 6.66 (s, 1H); 6.82 (t, 1H, NH); 7.31 (t, 2H); 7.63 (dd, 2H); 7.97 (d, 1H).

MS (e/z) ESI: 465.3 (MH<sup>+</sup>).

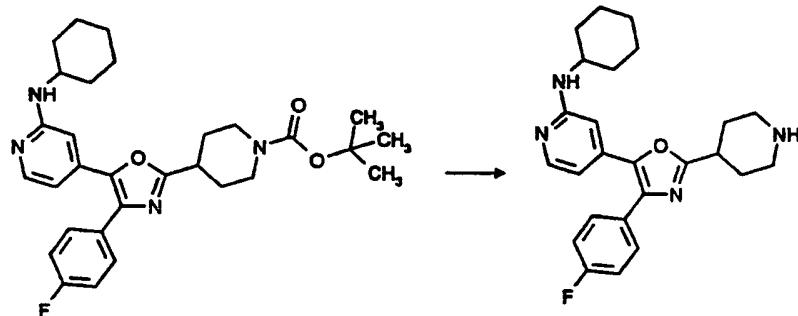
Example 21: 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole

a) 4-(4-Fluorophenyl)-2-(4-N-tert.butylox carbonyl)piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole



4-(4-Fluorophenyl)-2-(4-N-tert.butylox carbonyl)piperidine-1-yl)-5-(2-fluoro-4-pyridyl)oxazole (100 mg; 0.226 mmol) is refluxed in cyclohexylamine (2 ml) for 4h, evaporated and purified by SiO<sub>2</sub> chromatography (TBME/hexanes 4/6) to yield the title compound (74 mg; 63%).

b) 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole

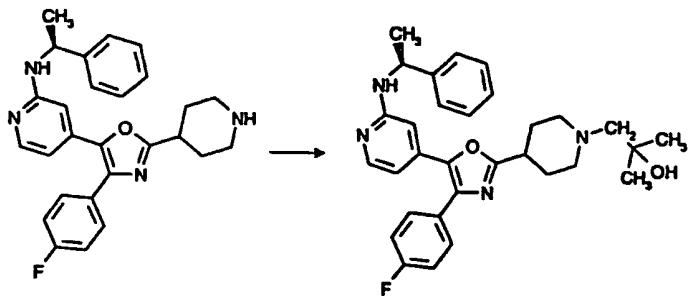


4-(4-Fluorophenyl)-2-(4-N-tert.butylox carbonyl)piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole (70 mg; 0.13 mmol) is treated analogously as for compound 14 to yield the title compound as pale yellow crystals (41 mg; 74%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6): 1.11-1.33 (m, 5H); 1.53-1.75 (m, 5H); 1.97 (bd, 2H); 1.96 (bd, 2H); 2.05-2.21 (bs, 1H, NH); 2.61 (dt, 2H); 2.92-3.03 (m, 3H); 3.53-3.65 (m, 1H); 6.47 (d, 1H); 6.58 (d, 1H, NH); 6.61 (s, 1H); 7.30 (t, 2H); 7.63 (dd, 2H); 7.95 (d, 1H).

MS (e/z) ESI: 421.3 (MH<sup>+</sup>, 70).

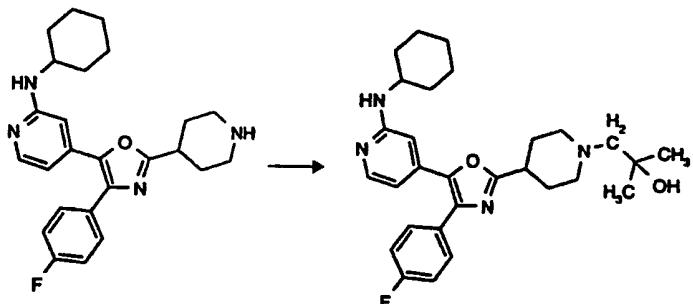
**Example 22: 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-(1-(S)-phenyl ethyl)amino-4-pyridyl)oxazole**



4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole (45 mg; 0.11 mmol) is treated analogously as for compound 14 with isobutylene oxide to render the title compound (34 mg; 66%) as a colorless foam.

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): 1.11 (s, 6H); 1.42 (d, 3H); 1.83 (bq, 2H); 1.98 (bd, 2H); 2.22 (s, 2H); 2.28 (bt, 2H); 2.81-2.91 (m, 1H); 2.99 (bd, 2H); 4.07 (s, 1H, OH); 4.90-5.02 (m, 1H); 6.48 (d, 1H); 6.67 (s, 1H); 7.15-7.24 (m, 2H); 7.25-7.33 (m, 6H); 7.60 (dd, 2H); 7.92 (d, 1H). MS (e/z) EI: 499 (M-CH<sub>3</sub>, 5); 455 (100).

**Example 23: 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole**

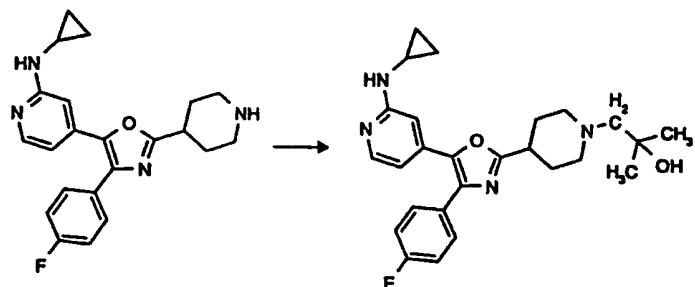


The title compound is prepared according to the procedure above and obtained as colorless crystals in 95% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 1.21. (s, 6H); 1.12-1.42 (m, 6H); 1.62-1.71 (m, 1H); 1.71-1.81 (m, 2H); 1.95-2.16 (m, 5H); 2.39 (s, 2H); 2.52 (t, 2H); 2.85-2.95 (m, 1H); 3.05 (bd, 2H); 3.18 (s, 1H, OH); 3.31-3.42 (m, 1H); 4.50 (d, 1H, NH); 6.45 (s, 1H); 6.70 (d, 1H); 7.12 (t, 2H); 7.63 (dd, 2H); 8.05 (d, 1H).

MS (e/z) ESI: 493.4 (MH+, 20); 247.3 (100).

**Example 24: 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-cyclopropylamino-4-pyridyl)oxazole**

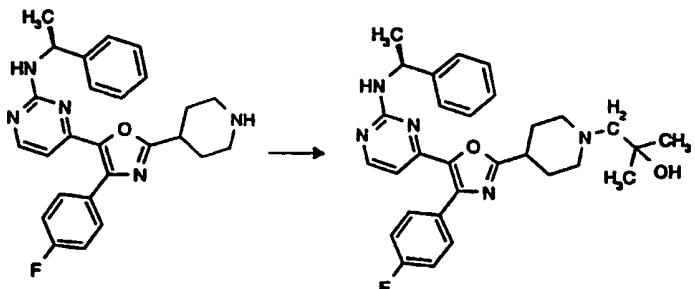


The title compound is prepared according to the procedure above and obtained as colorless crystals in 95% yield.

1H-NMR (400MHz; CDCl<sub>3</sub>): 0.52 (bq, 2H); 0.68 (bq, 2H); 1.21 (s, 6H); 2.00-2.20 (m, 4H); 2.40 (s, 3H); 2.53 (bt, 2H); 2.88-2.98 (m, 1H); 3.04 (bd, 2H); 3.20 (s, 1H, OH); 5.03 (s, 1H, NH); 6.83 (d, 1H); 6.88 (s, 1H); 7.13 (t, 2H); 7.67 (dd, 2H); 8.08 (d, 1H).

MS (e/z) ESI: 451.2 (MH<sup>+</sup>, 25); 226.1 (100); 217.2 (50).

**Example 25: 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)oxazole**



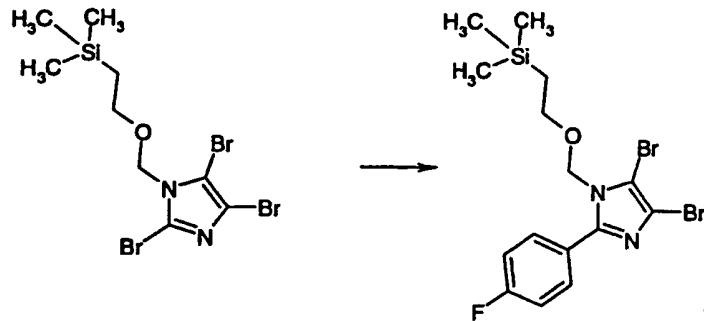
The title compound is prepared according to the procedure above from 4-(4-fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole (Example 7) and obtained as colorless crystals in 85% yield.

1H-NMR (400MHz; CDCl<sub>3</sub>): 1.18 (s, 6H); 1.52 (d, 3H); 1.98-2.17 (m, 4H); 2.38 (s, 2H); 2.52 (bt, 2H); 2.87-2.97 (m, 1H); 3.05 (d, 2H); 3.16 (bs, 1H, OH); 5.08 (bs, 1H); 5.40 (d, 1H, NH); 6.85 (d, 1H); 7.07 (t, 2H); 7.23-7.36 (m, 5H); 7.95 (dd, 2H); 8.32 (d, 1H).

MS (e/z) ESI: 516.3 (MH<sup>+</sup>, 75); 258.7 (100).

**Example 26: 3-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole**

a) **4,5-Dibromo-2-(4-fluorophenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole**

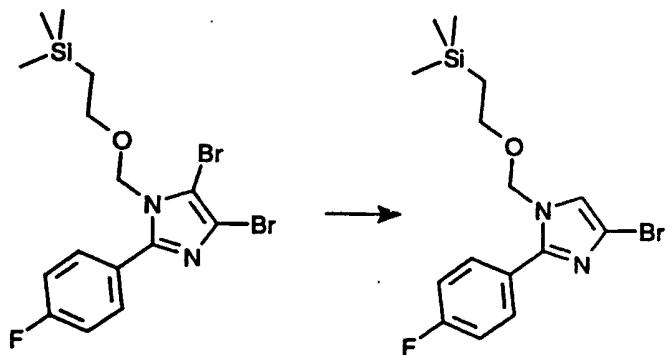


2,4,5-Tribromo-1-(2-trimethylsilyl-ethoxymethyl)imidazole (Tetrahedron Lett. (1998), 39(29), 5171-5174) (12.2 g; 28.2 mmol), 4-fluorophenyl-boronic acid (4.34 g; 31.02 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.6 g; 1.4 mmol) are dissolved in 1,2-dimethoxy-ethane (122 ml) and saturated Na<sub>2</sub>CO<sub>3</sub> solution (36.5 ml) and refluxed for 24 h. Water is added to the reaction mixture and the aqueous phase extracted three times with ethyl acetate. The combined organic phases are washed with 2N Na<sub>2</sub>CO<sub>3</sub> and saturated NaCl-solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (Cyclohexane/EtOAc 99.7:0.3 > 90:10) yields the desired product as a white solid (9.9 g; 78%).

1H-NMR (400MHz; DMSO-d6): 0.00 (s, 9H); 0.85 (t, 2H); 3.52 (t, 2H); 5.33 (s, 2H); 7.39 (dd, 2H); 7.78 (dd, 2H).

MS (m/z) EI: 450 (MH<sup>+</sup>; 20).

b) **4-Bromo-2-(4-fluorophenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole**

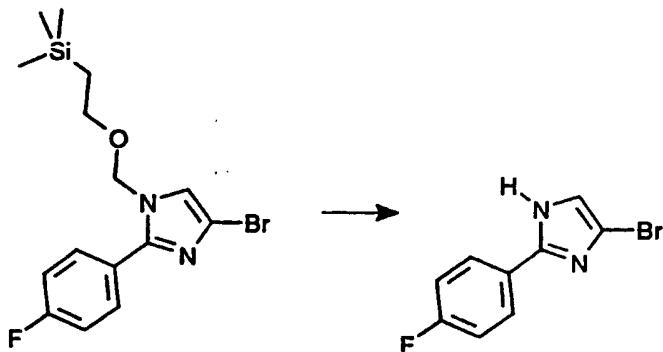


4,5-Dibromo-2-(4-fluorophenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole (10.8 g; 25 mmol) are dissolved in THF (108 ml) and cooled to -78°C under argon. N-BuLi (15.6 ml; 1.6 M) is added under stirring within 15 min. After 30 min at -78 °C, isopropanol (7.8 ml; 0.1 mol) is introduced dropwise and the mixture warmed to room temperature. Water is added to the reaction mixture and the aqueous phase extracted three times with ethyl acetate. The combined organic phases are washed with saturated NaCl-solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness, yielding the title compound as colorless oil (9.1 g; 95%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): 0.00 (s, 9H); 0.86 (t, 2H); 3.58 (t, 2H); 5.33 (s, 2H); 7.35 (dd, 2H); 7.68 (s, 1H); 7.82 (dd, 2H).

MS (m/z) EI: 372 (M<sup>+</sup>).

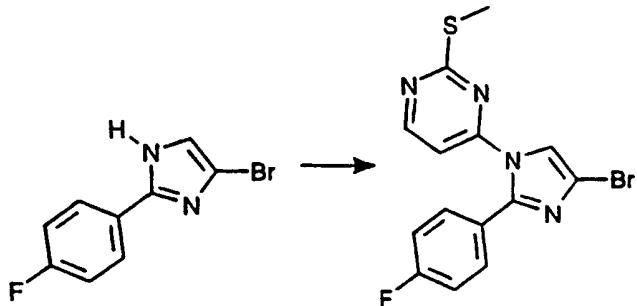
**c) 4-Bromo-2-(4-fluorophenyl)-1-H-imidazole**



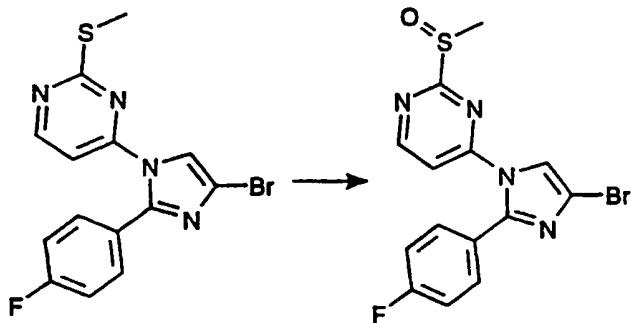
4-Bromo-2-(4-fluorophenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole (3.4 g; 9 mmol) is dissolved in EtOH (34 ml) and HCl conc. (37%; 34 ml) and heated to 55 °C for 1 h. Water is added to the reaction mixture and the aqueous phase extracted three times with ethyl acetate. The combined organic phases are washed with 2N Na<sub>2</sub>CO<sub>3</sub> and saturated NaCl-solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound as colorless crystals (2.1 g; 92 %).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): 7.32 (dd, 2H); 7.42 (s, 1H); 7.93 (dd, 2H).

MS (m/z) EI: 242 (M<sup>+</sup>; 90), 240 (90), 161 (75), 134 (100), 107 (60).

d) 4-Bromo-2-(4-fluorophenyl)-1-(4-(2-methylthio)pyrimidyl)imidazole

4-Bromo-2-(4-fluorophenyl)-1-H-imidazole (1.2 g; 4.9 mmol) is dissolved in DMF (20 ml) and cooled to 0C under argon. KN(TMS)<sub>2</sub> (10.5 ml of a 0.5 M solution in toluene; 5.22 mmol) is added dropwise under stirring. After stirring for 15 min at 0 C, 4-chloro-2-methylthiopyrimidine (837 mg; 5.22 mmol) in DMF (1 ml) is added dropwise and the reaction mixture gradually warmed to room temperature and heated at 80 C for 12 h. The reaction mixture is poured on saturated NaCl solution and extracted with TBME three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, evaporated to dryness and purified by SiO<sub>2</sub> chromatography (TBME/hexanes 2:8 to 3:7) to yield the title compound as yellow crystals (1.35 g; 74%).  
<sup>1</sup>H-NMR (400MHz; DMSO-d6): 2.15 (s, 3H); 7.18 (d, 1H); 7.27 (dd, 2H); 7.48 (dd, 2H); 8.10 (s, 1H); 8.72 (d, 1H).  
MS (m/z) CI: 365 (100); 363 (M+; 100).

e) 4-Bromo-2-(4-fluorophenyl)-1-(4-(2-methylsulfinyl)pyrimidyl)imidazole

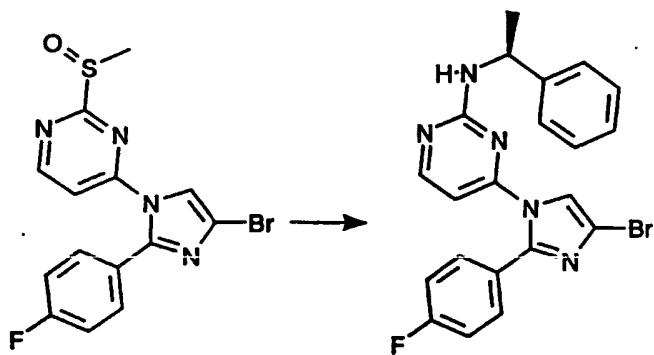
4-Bromo-2-(4-fluorophenyl)-1-(4-(2-methylthio)pyrimidyl)imidazole (1.35 g; 3.7 mmol) is dissolved in methylene chloride (20 ml) and cooled to 0 C. mCPBA (70% in water; 1.18 g; 4.8 mmol) dissolved in methylene chloride (10 ml) is added dropwise and stirring continued for 5

min at 0 C. The reaction mixture is poured on saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with ethyl acetate three times. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness yielding the title compound as light brown foam (1.3 g; 92%) which was used for the next step without further purification.

<sup>1</sup>H-NMR (400MHz; DMSO-d6): 2.70 (s, 3H); 7.28 (dd, 2H); 7.53 (dd, 2H); 7.58 (d, 1H); 8.18 (s, 1H); 9.10 (d, 1H)

MS (m/z) EI: 382 (100; M+), 380 (100).

**f) 4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole**

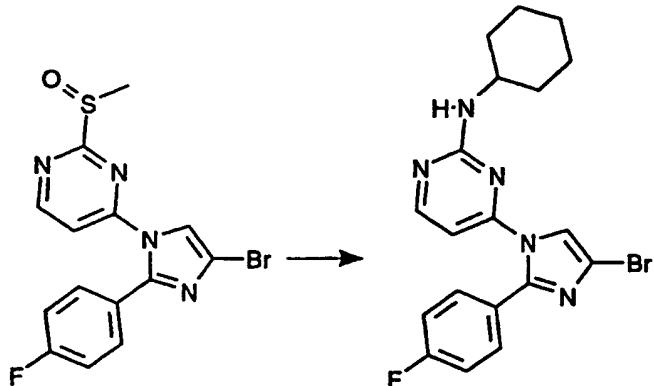


4-Bromo-2-(4-fluorophenyl)-1-(4-(2-methylsulfinyl)pyrimidyl)imidazole (1.3 g; 3.4 mmol) is dissolved in S-(-)-1-phenylethylamine (6ml) and heated at 120 C for 15 min. After evaporation of the amine, the residue is purified by SiO<sub>2</sub> chromatography (TBME/hexanes 4:6) to yield the title compound as pale brown foam (0.94 g; 62%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6: tautomeric mixture with broad signals. 1.28 (bs, 1.8H); 1.42 (bs, 1.2H); 4.42 (bs, 0.7H); 5.13 (bs, 0.3H); 6.38 (bs, 0.3H); 6.5 bs, 0.7H); 7.15-7.32 (m, 7H); 7.45 (bt, 2H); 7.80 (bs, 1H); 8.10 (bd, 1H); 8.47 (bs, 1H).

MS (m/z) EI: 382 (100; M+), 380 (100).

**Example 27: 4-Bromo-2-(4-fluoromethylphenyl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole**

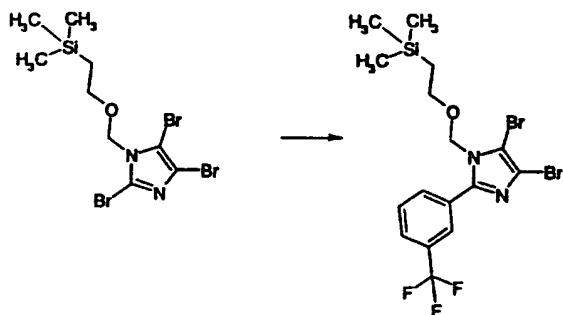


The title compound is prepared according to the procedure described above and obtained as colorless crystals in 76% yield.

**Example 28:**

Similar to Example 26 a) to f) above a 2-(3-trifluoromethylphenyl)- product and corresponding intermediates are prepared according to the procedure described above.

**a) 4,5-Dibromo-2-(3-trifluoromethylphenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole**

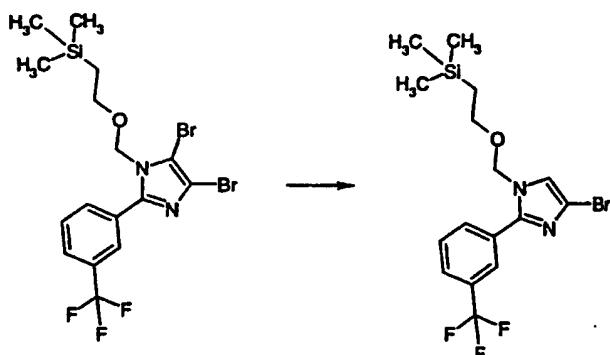


The title compound is prepared according to the procedure above using 3-trifluoromethylphenylboronic acid and obtained as a viscous oil in 64% yield after purification over  $\text{SiO}_2$ .

$^1\text{H-NMR}$  (200MHz;  $\text{CDCl}_3$ ): 0.00 (s, 9H); 0.98 (t, 2H); 3.70 (t, 2H); 5.25 (s, 2H); 7.57 (t, 1H); 7.69 (d, 1H); 8.01 (d, 1H); 8.12 (d, 1H).

MS (m/z) EI: 500 (M+; 20), 457 (70), 442 (50), 376 (25), 350 (20), 103 (35).

b) 4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-trimethylsilyl-ethoxymethyl)imidazole.

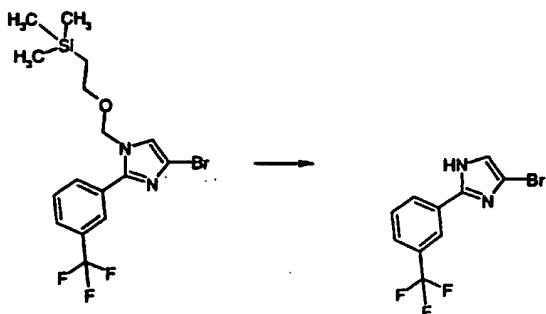


The title compound is prepared according to the procedure above, obtained as a viscous oil in quantitative yield and used in the next step without further purification.

<sup>1</sup>H-NMR (200MHz; CDCl<sub>3</sub>): 0.00 (s, 9H); 0.96 (t, 2H); 3.61 (t, 2H); 5.22 (s, 2H); 7.10 (s, 1H); 7.57 (dd, 1H); 7.68 (d, 1H); 8.00 (d, 1H); 8.10 (s, 1H).

MS (m/z) CI: 424 (20), 423 (80), 422 (40), 421 (MH+; 90), 403 (100), 401 (95), 393 (80), 391 (60), 378.9 (80), 376.9 (80), 364.9 (100), 362.9 (100).

c) 4-Bromo-2-(3-trifluoromethylphenyl)-1-H-imidazole

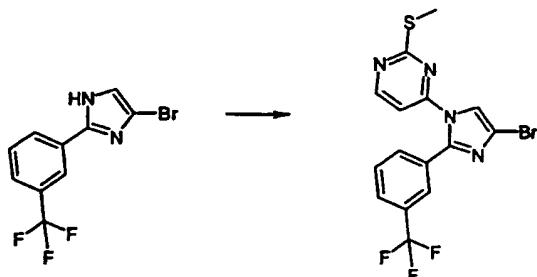


The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 94% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 7.17 (s, 1H); 7.58 (dd, 1H); 7.65 (d, 1H); 8.02 (d, 1H); 8.10 (s, 1H).

MS (m/z) ESI: 292 (M+1; 100), 291 (M+; 100).

**d) 4-Bromo-2-(3-trifluoromethylphenyl)-1-(4-(2-methylthio)pyrimidyl)imidazole**

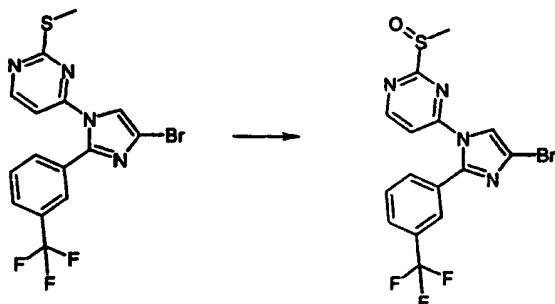


The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 61.3% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 2.40 (s, 3H); 6.58 (d, 1H); 7.55 (dd, 1H); 7.61 (d, 1H); 7.67 (s, 1H); 7.73 (d, 1H); 7.85 (s, 1H); 8.49 (d, 1H).

MS (m/z) EI: 416 (M+, 100); 414 (100); 335 (60); 164 (45).

**e) 4-Bromo-2-(3-trifluoromethylphenyl)-1-(4-(2-methylsulfinyl)pyrimidyl)imidazole**

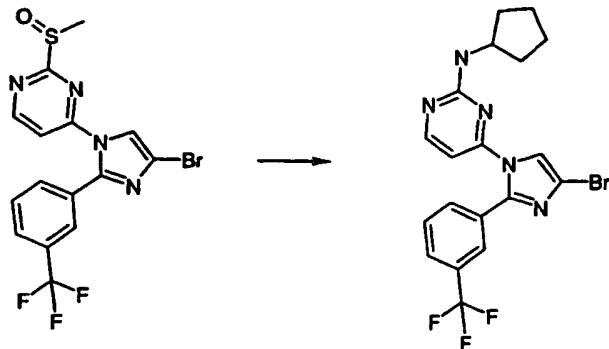


The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 90% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 2.92 (s, 3H); 6.97 (d, 1H); 7.58-7.68 (m, 2H); 7.78 (d, 1H); 7.83 (bs, 2H); 8.84 (d, 1H).

MS (m/z) CI: 433 (98); 431 (M+, 100); 413 (80); 411 (75).

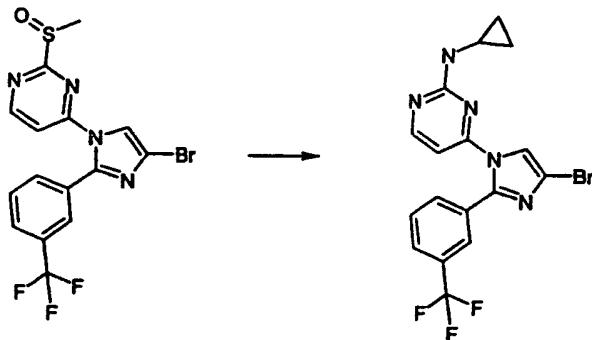
**f) 4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole**



The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 78% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 1.30-2.22 (m, 8H); 3.75-4.00 (bs, 1H); 5.10-5.45 (bs, NH, 1H); 6.17 (bs, 1H); 7.51 (dd, 1H); 7.55 (s, 1H); 7.65 (d, 1H); 7.69 (d, 1H); 7.86 (s, 1H); 8.23 (d, 1H).  
MS (m/z) EI: 452 (M+, 100); 450 (100); 384 (70); 382 (70); 372 (30); 304 (35); 94 (85).

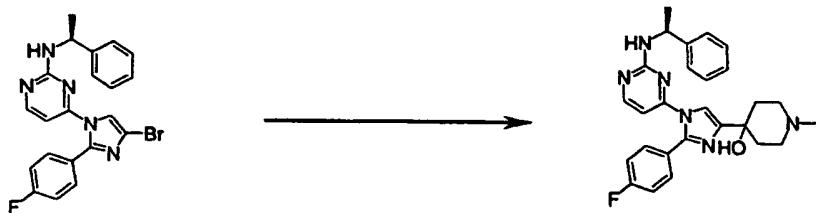
**Example 29: 4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole**



The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 73% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 0.50 (bs, 2H); 0.78 (bs, 2H); 2.52-2.77 (bs, 1H); 5.50 (bs, 1H); 6.24 (d, 1H); 7.52 (dd, 1H); 7.58 (s, 1H); 7.67 (d, 1H); 7.71 (d, 1H); 7.88 (s, 1H); 8.30 (d, 1H).  
MS (m/z) CI: 426 (98); 424 (M+, 100); 406 (23); 404 (25).

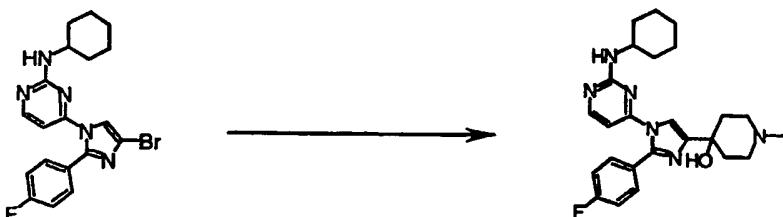
**Example 30: 2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole**



4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole (100 mg; 0.228 mmol) are dissolved in THF (1.4 ml) and cooled to - 78 °C under argon. BuLi (0.29 ml of a 1.6 M solution in hexane; 0.456 mmol) is introduced and stirring continued for 10 min., N-methyl-4-piperidone (0.027 ml; 0.228 mmol) is added at - 78 °C and after 2 min the reaction mixture is poured on saturated NaCl solution and extracted with TBME three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification via SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub>conc. 90/10/1 to 80/20/1) yielded the title compound as colorless crystals (20 mg; 19%).

1H-NMR (400MHz; DMSO-d6, 120 °C): 1.42 (d, 3H); 2.00 (bd, 2H); 2.23-2.35 (m, 2H); 2.70 (s, 3H; NMe); 3.12 (bs, 4H); 4.78-4.91 (m, 2H); 6.32 (d, 2H); 7.11-7.50 (m, 9H); 8.27 (d, 1H). MS (m/z) EI: 472 (M+); 454 (100); 402 (40); 359 (20); 105 (60); 71 (95).

**Example 31: 2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole**

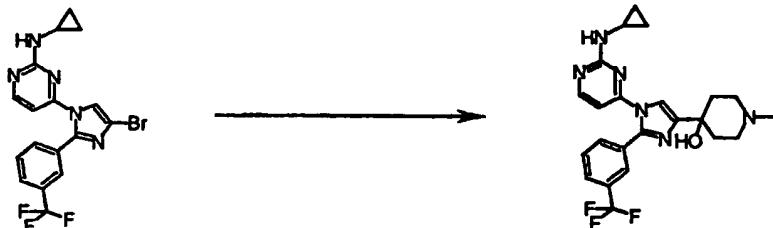


The title compound is prepared according to the procedure described above and obtained as slightly yellow crystals in 46% yield.

1H-NMR (400MHz; DMSO-d6, 120 °C): 1.15-1.28 (m, 6H); 1.48 (m, 1H); 1.65-1.82 (m, 6H); 2.08-2.18 (m, 3H); 2.22 (s, 3H); 2.30-2.40 (m, 1H); 2.42-2.50 (m, 1H); 3.42 (m, 1H); 4.03 (bs, 1H, OH); 6.37 (d, 1H); 6.58 (bd, 1H, NH); 7.15 (d, 1H); 7.18 (d, 1H); 7.43-7.49 (m, 3H); 8.26 (d, 1H).

MS (m/z) EI: 449 (M-1, 100).

**Example 32: 2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole**

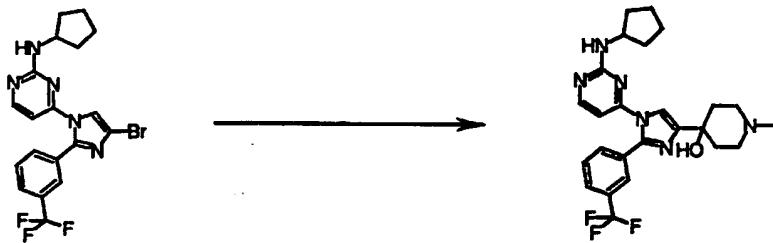


The title compound is prepared according to the procedure described above (except that a 4:1 THF/isopentane mixture was used as solvent and nBuLi was added at -100°C) and obtained as colorless crystals in 43% yield.

<sup>1</sup>H-NMR (400MHz; CDCl<sub>3</sub>): 0.50 (bs, 2H); 0.78 (bs, 2H); 1.78 (bs, 1H); 2.05 (bd, 2H); 2.12-2.23 (m, 2H); 2.48 (s, 3H); 2.57 (bt, 2H); 2.69-2.82 (m, 3H); 5.50 (bs, 1H, NH); 6.22 (d, 1H); 7.43 (s, 1H); 7.53 (dd, 1H); 7.67 (t, 2H); 7.83 (s, 1H); 8.28 (d, 1H).

MS (m/z) Cm/ES-: 457 (M-1, 100). MS (m/z) Cm/ES+: 459 (MH+, 100).

**Example 33: 2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole**

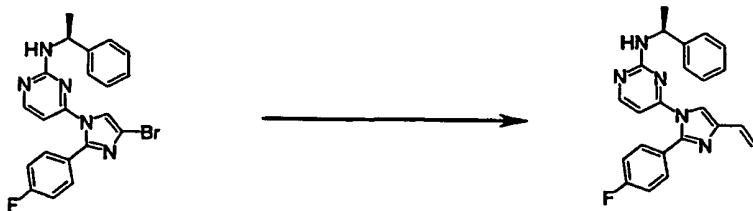


The title compound is prepared according to the procedure described above (THF/isopentane mixture was used as solvent and nBuLi was added at -100°C) and obtained as colorless viscous oil in 42% yield. Crystallisation as fumarate salt was performed from acetone providing colorless crystals with m.p. 189-193°C.

<sup>1</sup>H-NMR of fumarate (400MHz; DMSO-d6, 120°C): 1.32-1.50 (m, 3H); 1.60-1.77 (m, 3H); 1.85 (bd, 2H); 2.18 (m, 2H); 2.32 (s, 3H); 2.53-2.67 (m, 4H); 3.78 (m, 1H); 6.48 (d, 1H); 6.63 (s, 2H, CH f fumarate); 6.78 (m, 1H); 7.51 (s, 1H); 7.61 (bt, 1H); 7.71 (bt, 2H); 8.31 (d, 1H).

MS (m/z) C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>: 487 (MH<sup>+</sup>, 40); 469 (100), 426 (15).

**Example 34: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-vinylimidazole**

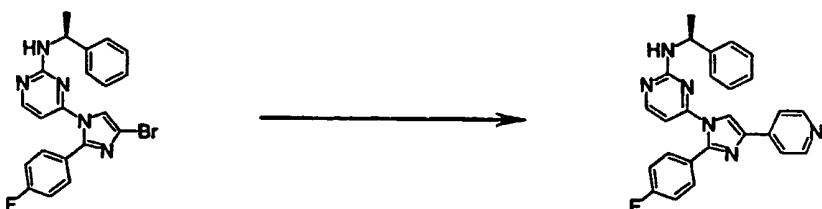


4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole (109 mg; 0.25 mmol), vinyltributylstannane (95 mg; 0.3 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (17 mg; 0.025 mmol) are dissolved in xylenes (5 ml) and refluxed for 3h. After filtration and evaporation, the reaction mixture is purified by preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min. to yield the title product as white foam (35 mg; 36%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>, 120 C): 1.41 (d, 3H); 4.88 (m, 1H); 5.19 (dd, 1H); 5.83 (dd, 1H); 6.32 (d, 1H); 6.65 (dd, 1H); 7.13-7.21 (m, 3H); 7.25-7.32 (m, 4H); 7.39 (bd, 1H); 7.47-7.51 (m, 2H); 7.58 (s, 1H); 8.27 (d, 1H).

MS (m/z) ESI: 386.2 (MH<sup>+</sup>).

**Example 35: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(4-pyridyl)-imidazole**



4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole (1.0 g; 2.28 mmol), 4-trimethylstannylpyridine (660 mg; 2.74 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (160 mg; 0.228 mmol) are dissolved in xylenes (23 ml) and refluxed for 4 h. The reaction mixture is poured on saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with ethyl acetate three times. The combined organic phases were

dried over  $\text{Na}_2\text{SO}_4$ , filtered, evaporated to dryness and purified via  $\text{SiO}_2$  chromatography (TBME/MeOH/NH<sub>3</sub>, conc 99/9/0.1) to yield the title compound as a yellow foam (780 mg; 68%).  
1H-NMR (400MHz; DMSO-d6): mixture of rotamers, broad signals: 1.30 (bs, 2.1H); 1.45 (bs, 0.9H); 4.45 (bs, 0.7H); 5.18 (bs, 0.3H); 6.48 (0.3H); 6.56 (bs, 0.7H); 7.20 (bd, 2H); 7.26-7.32 (m, 5H); 7.53 (bs, 2H); 7.32 (bs, 2H); 8.15 (d, 1H); 8.40 (bs, 2H); 8.60 (d, 2H).  
MS (m/z) EI: 436 (M+, 100); 421 (95);

The compounds of Examples 36 to 39 and the precursor a) of Example 40 are similarly prepared by coupling 4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole with heteroarylstannanes as described above:

**Example 36: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-pyridyl)-imidazole**

1H-NMR (400MHz; DMSO-d6, mixture of rotamers at room temperature): 1.25-1.36 (bd, 3H); 4.45 (bs, 1H); 6.62 (bs, 1H); 7.15-7.32 (m, 8H); 7.55 (bs, 2H); 7.86 (dt, 1H); 7.98 (d, 1H); 8.07 (d, 1H); 8.20 (bs, 1H); 8.35 (bs, 1H); 8.58 (d, 1H).  
MS (m/z) EI: 436 (M+, 100); 421 (60); 240 (20); 225 (40); 211 (30); 105 (30).

**Example 37: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(3-pyridyl)-imidazole**

1H-NMR (400MHz; DMSO-d6, 120°C): 1.48 (d, 3H); 4.88 (m, 1H); 6.42 (d, 1H); 7.19 (t, 3H); 7.23-7.33 (m, 4H); 7.41 (m, 2H); 7.50-7.53 (m, 2H); 8.08 (s, 1H); 8.16 (dd, 1H); 8.31 (d, 1H); 8.48 (dd, 1H); 9.06 (d, 1H).  
MS (m/z) EI: 436 (M+, 90); 421 (60).

**Example 38: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-thienyl)-imidazole**

1H-NMR (400MHz; DMSO-d6, 120°C): 1.45 (d, 3H); 4.89 (m, 1H); 6.38 (d, 1H); 7.10 (dd, 1H); 7.20 (m, 3H); 7.28-7.36 (m, 3H); 7.38-7.48 (m, 3H); 7.50-7.55 (m, 2H); 7.82 (s, 1H); 8.30 (d, 1H).  
MS (m/z) ESI: 442 (MH+, 100).

**Example 39: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-furyl)-imidazole**

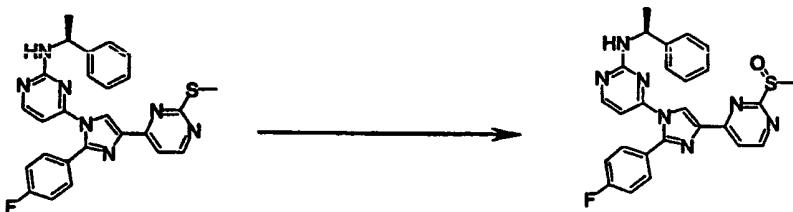
1H-NMR (400MHz; DMSO-d<sub>6</sub>, 120°C): 1.42 (d, 3H); 4.90 (m, 1H); 6.40 (d, 1H); 6.52 (s, dd 1H); 6.68 (d, 1H); 7.20 (t, 3H); 7.25-7.35 (m, 4H); 7.52 (m, 2H); 7.61 (d, 1H); 7.78 (s, 1H); 8.30 (d, 1H).

MS (m/z) ESI: 426 (MH<sup>+</sup>, 100).

**Example 40: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-amino)pyrimidylimidazole**

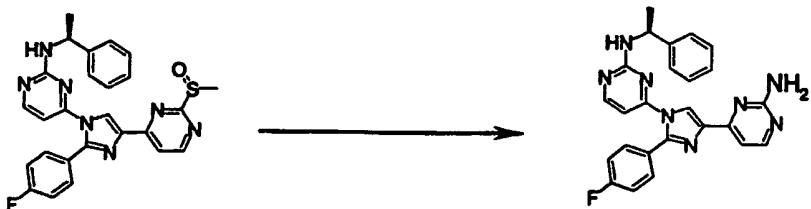
**a) 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-methylthio)pyrimidylimidazole**

**b) 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-methylsulfinyl)pyrimidylimidazole**



2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-methylthio)pyrimidylimidazole (483 mg; 1 mmol) is dissolved in methylene chloride (24 ml) and treated at 0 C with mCPBA (70% in water; 286 mg; 1.4 mmol) in methylene chloride (2.9 ml). After 30 min at 0 C the reaction mixture is poured on 2N Na<sub>2</sub>CO<sub>3</sub> and extracted with methylene chloride three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness yielding the sulfoxide as a pale yellow foam (530 mg), which is used without further purification.

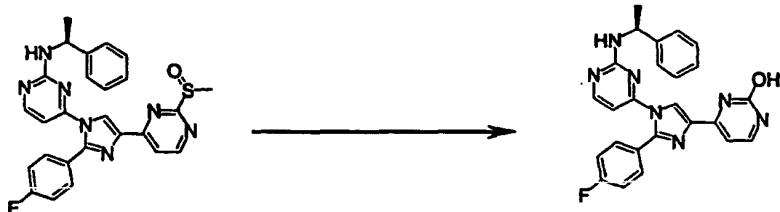
**c) 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-amino)pyrimidylimidazole**



2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-methylsulfinyl) pyrimidyl-imidazole (50 mg; 0.1 mmol) is transferred into a steel cylinder, dissolved in THF (10 ml), cooled to -78 °C and saturated with NH<sub>3</sub>. The reaction mixture is heated to 80 °C for 3 h and gives after evaporation of the solvent and purification by preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min the title product as colorless crystals (13 mg; 31%).

MS (m/z) EI: 453 (30); 452 (M+, 100); 437 (70).

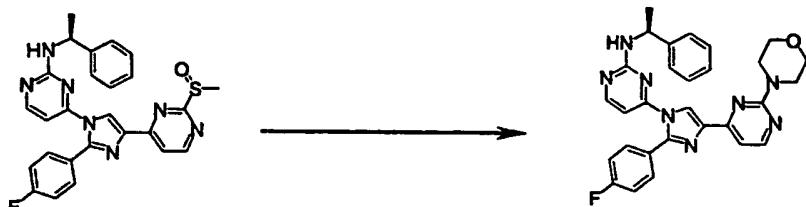
**Example 41: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-hydroxy)pyrimidylimidazole**



The sulfoxide (50 mg; 0.1 mmol) is dissolved in dioxan/water (5 ml 5/1) and treated with 3 N KOH (0.1 ml) for 1 h at room temperature. The reaction mixture is acidified with 2 N HCl and extracted twice with ethyl acetate. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, evaporated to dryness and purified by preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min to yield the title product as colorless crystals (20 mg; 44%).

1H-NMR (400MHz; DMSO-d6, 120 °C): 1.44 (s, 3H); 4.85-4.92 (m, 1H); 6.48 (d, 1H); 6.97 (d, 1H); 7.17-7.23 (m, 3H); 7.28-7.35 (m, 4H); 7.48-7.58 (m, 3H); 7.96 (bd, 1H, NH); 8.33 (d, 2H).  
 MS (m/z) EI: 453 (M+, 100); 438 (75).

**Example 42: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-N-morpholinyl)pyrimidylimidazole**

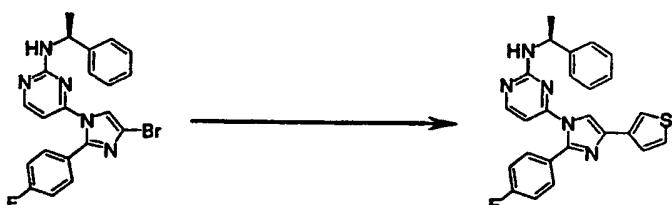


2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-methylsulfinyl) pyrimidylimidazole (50 mg; 0.1 mmol) and morpholine (0.5 ml) are heated at 80 C for 30 min. The reaction mixture is evaporated to dryness and purified by preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min to yield the title product as colorless crystals (25 mg; 48%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6): mixture of rotamers, broad signals: 1.31 (bs, 2.1H); 1.45 (bs, 0.9H); 3.72 (bs, 4H); 3.80 (bs, 4H); 4.48 (bs, 0.7H); 5.18 (bs, 0.3H); 6.29 (bs, 0.3H); 6.57 (bs, 0.7H); 7.13-7.43 (m, 8H); 7.50 (bs, 2H); 8.15 (d, 1H); 8.19-8.42 (m, 2H); 8.43 (d, 1H).

MS (m/z) EI: 522 (M+, 100); 492 (70); 491 (70); 477 (60); 465 (50); 105 (20).

**Example 43: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-thienyl)imidazole**



4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole (109 mg; 0.25 mmol), thiophene-3-boronic acid (35 mg; 0.27 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14 mg; 0.0125 mmol) are dissolved in dioxane (1.25 ml) and saturated Na<sub>2</sub>CO<sub>3</sub> solution (0.33 ml; 0.55 mmol) and heated to 80 C for 18 h. The reaction mixture is poured on saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with ethyl acetate three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated and purified via preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min to yield the title product as colorless crystals (62 mg; 60%).

1H-NMR (400MHz; DMSO-d<sub>6</sub>, 120 C): 1.41 (d, 3H); 4.82-4.93 (m, 1H); 6.40 (d, 1H); 7.16-7.22 (m, 3H); 7.26-7.35 (m, 4H); 7.40 (d, 1H, NH); 7.50-7.58 (m, 4H); 7.71 (d, 1H); 7.84 (s, 1H); 8.30 (d, 1H).

MS (m/z) EI: 441 (M+, 100); 426 (40).

The following compounds of Examples 44 to 49 are similarly prepared by coupling 4-bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole with aryl and heteroaryl boronic acids:

**Example 44: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(2-benzofuryl)imidazole**

**Example 45: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(5-chlorothien-2-yl)imidazole**

**Example 46: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-methoxyphenyl)imidazole**

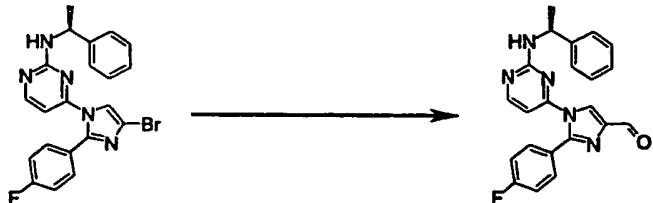
**Example 47: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-fluorophenyl)imidazole**

**Example 48: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chloro-4-fluorophenyl)imidazole**

**Example 49: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chlorophenyl)imidazole (AAL395)**

**Example 50: 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-methyleneaminoguanidinyl-imidazole**

a) **2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-formyl)-imidazole**

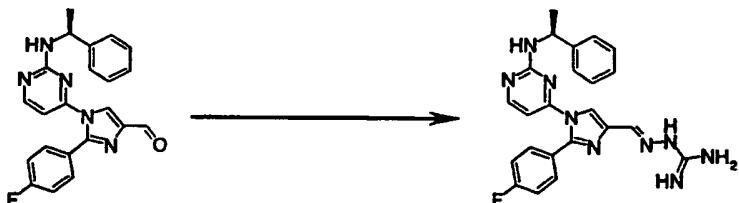


4-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole (200 mg; 0.45 mmol) is dissolved in THF (2.8 ml), cooled to -78 C and treated with nBuLi (0.57 ml of a 1.6 M solution in hexane; 0.9 mmol) for 10 min. Dimethylformamide (0.039 ml; 0.5 mmol) is added and stirred for 10 min. The reaction mixture is poured on saturated NaCl solution and extracted with TBME three times. The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated and purified via preparative HPLC on LiChrospher RP-18 (Gilson HPLC-system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min to yield the title product as white foam (36 mg; 20%).

1H-NMR (400MHz; DMSO-d6): mixture of rotamers, broad signals: 1.30 (bs, 2.1H); 1.45 (bs, 0.9H); 4.45 (bs, 0.7H); 5.15 (bs, 0.3H); 6.45 (bs, 0.3H); 6.58 (bs, 0.7H); 7.12-7.21 (bd, 2H); 7.24-7.40 (m, 4H); 7.50 (bs, 2H); 8.18 (bd, 1H); 8.4 (bd, 1H, NH), 9.88 (s, 1H).

MS (m/z) EI: 387 (M+, 100); 372 (85), 105 (25).

b) **2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-methyleneaminoguanidinyl-imidazole**



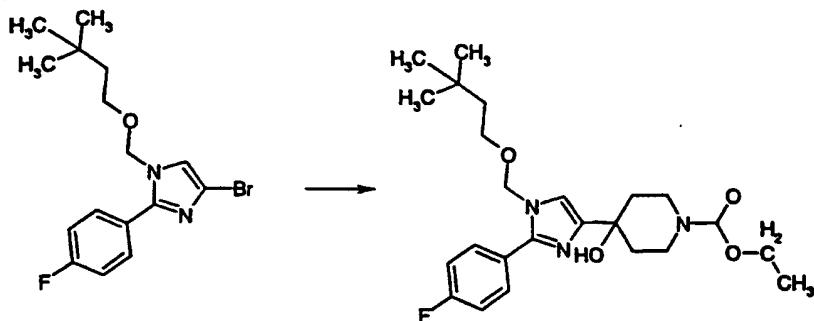
2-(4-Fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-4-(3-formyl)imidazole (26 mg; 0.068 mmol) is dissolved in EtOH (0.5 ml) and 5.5 N HCl in isopropanol (0.5 ml) and treated with aminoguanidine-hydrogencarbonate (18.5 mg; 0.13 mmol). The reaction mixture is diluted with MeOH (1.5 ml) and left at room temperature over night and is poured on saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with ethyl acetate three times. The combined organic phases are dried over

$\text{Na}_2\text{SO}_4$ , filtered and evaporated and purified via  $\text{SiO}_2$  chromatography (TBME/MeOH/ $\text{NH}_3$ conc 80/20/2) to yield the title compound as white crystals (7 mg; 23%).

MS (m/z) EI: 443 ( $M^+$ , 100); 246 (50); 105 (65).

**Example 51: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-ethoxycarbonyl)piperidine-1-yl imidazole**

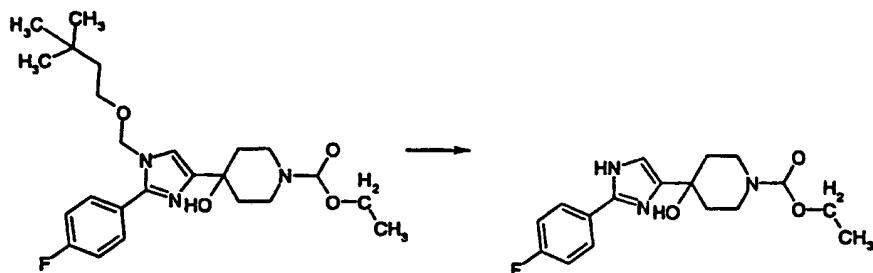
**a) 4-(4-Ethoxycarbonyl-1-hydroxypiperidine-1-yl)-2-(4-fluorophenyl)-1-(2-(trimethylsilyl)ethoxymethylimidazole**



$n\text{BuLi}$  (8.25 ml of a 1.6 M solution in hexane; 13.2 mmol) is added under argon within 10 min to a precooled and stirred solution (-78 °C) of 4-bromo-2-(4-fluorophenyl)-1-(2-(trimethylsilyl)ethoxy-methyl)imidazole (4.45 g; 12 mmol) in THF (50 ml). Stirring is continued for 15 min at -78 °C. N-Ethoxycarbonyl-4-piperidone (2.35 ml; 15.6 mmol) is introduced within 2 min. After 30 min at -78 °C, the reaction mixture is warmed to 0 °C within 30 min, poured on ice-water and extracted three times with ethyl acetate. The combined organic phases are washed with a saturated solution of  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness. Purification over  $\text{SiO}_2$  (cyclohexane/acetone 99/1 to 92/8) yields the title compound (2.5 g; 45%) as colorless foam.

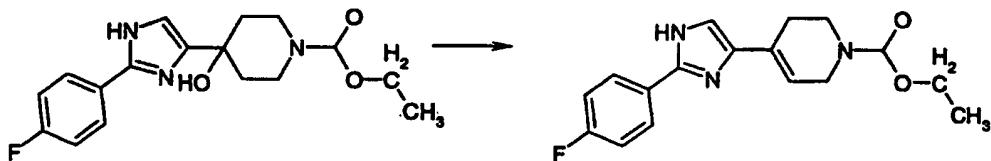
NMR: -0.03 (s, 9H); 0.86 (t, 2H); 1.19 (t, 3H); 1.66 (bd, 2H); 1.88-1.97 (m, 2H); 3.19-3.37 (bd, 2H); 3.58 (t, 2H); 3.72 (bd, 2H); 4.05 (q, 2H); 4.95 (s, 1H, OH); 5.31 (s, 2H); 7.30 (s, 1H); 7.32 (t, 2H); 7.80 (dd, 2H).

MS (m/z): 463 ( $M^+$ , 60); 435 (45); 335 (70); 277 (70); 189 (40); 73 (100).

**b) 4-(4-Ethoxycarbonyl-1-hydroxypiperidine-1-yl)-2-(4-fluorophenyl)-1H-imidazole**

2-(4-Fluorophenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-4-(4-ethoxycarbonyl-1-hydroxypiperidine-1-yl)imidazole (13.2 g; 28.6 mmol) dissolved in EtOH/HClconc (1:1; 290 ml) is heated at 50 C for 1 h, poured on 2N NH<sub>4</sub>OH and extracted three times with ethyl acetate. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound (11 g), which after recrystallization from TBME gave the product in high purity (4.7 g; 49%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): Tautomeric mixture. 1.21 (t, 3H); 1.68 (bd, 2H); 1.80-1.98 (m, 2H); 3.27 (bs, 2H); 3.69-3.83 (m, 2H); 4.06 (q, 2H); 4.85 (s, 1H, OH); 7.09 (s, 1H); 7.28 (dd, 2H); 7.93 (dd, 1.2H); 8.02 (dd, 0.8H); 12.20 (s, 0.6H, NH); 12.30 (s, 0.4H, NH).  
MS (m/z; ESI): 334.2 (MH<sup>+</sup>, 100).

**c) 4-(4-Ethoxycarbonylpiperid-1-ene-1-yl)-2-(4-fluorophenyl)-1H-imidazole**

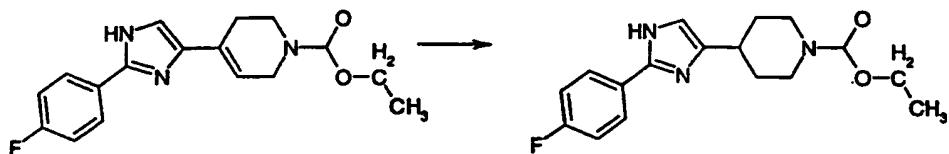
4-(4-Ethoxycarbonyl-1-hydroxypiperidine-1-yl)-2-(4-fluorophenyl)-1H-imidazole (4.6 g; 13.8 mmol), imidazole (1.13 g; 16.56 mmol), tert.-butyldimethylchlorsilane (2.5 g; 16.56 mmol) are dissolved in DMF (70 ml) and heated at 70 C for 24 h. The reaction mixture is evaporated, water added and the aqueous phase extracted with ethyl acetate three times. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated

to dryness to yield the crystalline product, which is purified by recrystallization from TBME and gives the title compound in high purity (3.1 g; 71%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): NMR: mixture of tautomers. 1.21 (t, 3H); 2.41 (bs, 2H); 3.60 (bt, 2H); 4.05 (bt, 2H); 4.10 (q, 2H); 6.24 (bs, 0.3H); 6.32 (bs, 0.7H); 7.30 (dd, 2H); 7.98 (dd, 1.4H); 8.05 (dd, 0.6H).

MS (m/z; EI): 315 (M+, 65); 286 (100); 242 (45).

**d) 4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1H-imidazole**

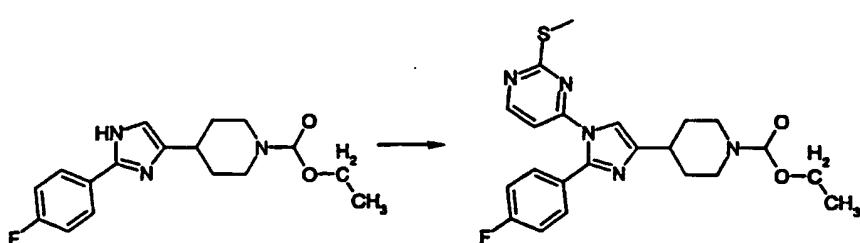


4-(4-Ethoxycarbonylpiperid-1-ene-1-yl)-2-(4-fluorophenyl)-1H-imidazole (3.7 g; 11.7 mmol) and 10 % Pd/C (0.9 g) are dissolved in acetic acid (117 ml) and hydrogenated until hydrogen uptake is complete (1 h). The reaction mixture is evaporated, 2N NH<sub>4</sub>OH added and the aqueous phase extracted with ethyl acetate three times. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the crystalline product (3.5 g; 96%), which is used without further purification.

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>): NMR: mixture of tautomers. 1.16-1.23 (m, 3H); 1.40-1.60 (m, 2H); 1.88-1.98 (m, 2H); 2.66-2.75 (m, 1H); 2.80-3.00 (m, 2H); 3.98-4.10 (m, 4H); 6.72 (s, 0.4H); 6.96 (s, 0.6H); 7.23-7.30 (m, 2H); 7.90-7.97 (m, 2H), 12.20 (s, 0.4H); 12.25 (s, 0.6H).

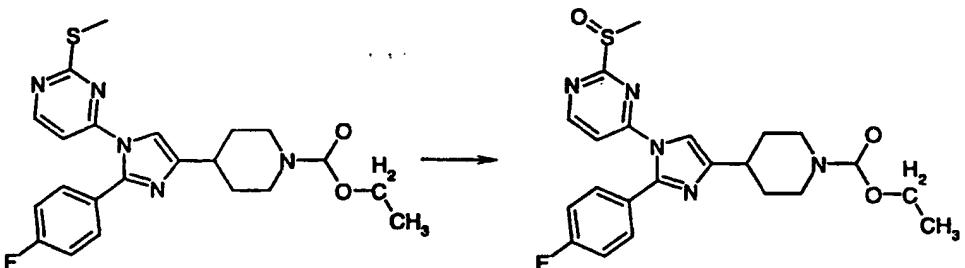
MS (m/z; EI): 317 (M+, 20); 244 (20); 189 (100).

**e) 4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1-((2-methylthio)-4-pyrimidyl)imidazole**



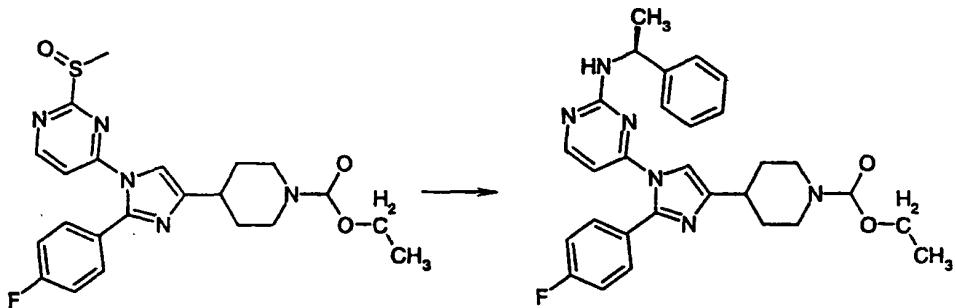
4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1H-imidazole (2.65 g; 8.4 mmol) is dissolved in DMF (53 ml) and cooled to 0 C. KN(TMS)2 (1.68 g; 9.24 mmol) in toluene (18.5 ml) is added at 0-10 C within 10 min and stirred for 30 min. 4-Chloro-2-methylthiopyrimidine (1.48 g; 9.24 mmol) in DMF (9 ml) is added at 10 C within 10 min and the reaction mixture stirred at room temperature for 1 h, then at 75 C for 18 h, poured on water and extracted three times with ethyl acetate. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (acetone/cyclohexane 1/9 to 3/7) yields the title compound as a yellow foam (2.6 g; 70%).  
<sup>1</sup>H-NMR (400MHz; DMSO-d6, 120C): 1.20 (t, 3H); 1.46-1.59 (dq, 2H); 1.95-2.03 (bd, 2H); 2.13 (s, 3H); 2.72-2.82 (tt, 1H); 2.86-3.03 (bs, 2H); 4.06 (q, 2H); 7.11 (d, 1H); 7.24 (t, 2H); 7.46 (dd, 2H); 7.63 (s, 1H); 8.68 (d, 1H).  
MS (m/z; EI): 441 (30); 368 (20); 313 (100).

f) 4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1-((2-methylsulfinyl)-4-pyrimidyl)imidazole



4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1-((2-methylthio)-4-pyrimidyl)imidazole (4.2 g; 9.52 mmol) is dissolved in methylene chloride (95 ml) and cooled to 0 C. mCPBA (70% in water, 2.6 g; 12.85 mmol) dissolved in methylene chloride (26 ml) is added within 15 min and the reaction mixture stirred for 15 min at 0 C. 2N Na<sub>2</sub>CO<sub>3</sub> (100 ml) is added and extracted three times with methylene chloride. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound (4.3g; 98%) which is used without further purification.

**g) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-ethoxycarbonyl)piperidine-1-yl imidazole**

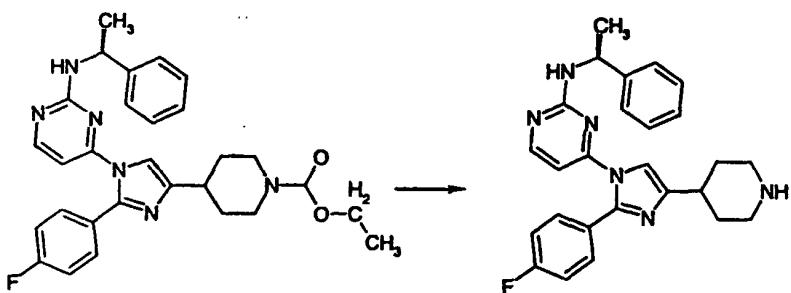


4-(4-Ethoxycarbonylpiperidine-1-yl)-2-(4-fluorophenyl)-1-((2-methylsulfinyl)-4-pyrimidyl)imidazole (4.3 g; 9.52 mmol) and 1-(S)-phenylethylamine (4.3 ml) are heated at 120 °C for 1h, evaporated to dryness and purified via SiO<sub>2</sub> chromatography (acetone/cyclohexane 1/9 to 2/8) to yield the title compound as colorless foam (4.4 g; 90%).

1H-NMR (400MHz; DMSO-d6) mixturs of rotamers. 1.19 (t, 3H); 1.3 (bd, 3H); 1.40-1.54 (bq, 2H); 1.93-2.01 (bd, 2H); 2.68-2.80 (bt, 1H); 2.96-3.03 (bs, 2H); 4.00-4.10 (m, 4H); 4.43 (bs, 0.7H); 5.13 (bs, 0.3H); 6.20 (bs, 0.3H); 6.48 (bs, 0.7H); 7.13-7.47 (m, 10H); 8.00 (d, 1H); 8.28 (bs, 1H, NH).

MS (m/z; ESI): 515.3 (M+,100).

**Example 52: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole**



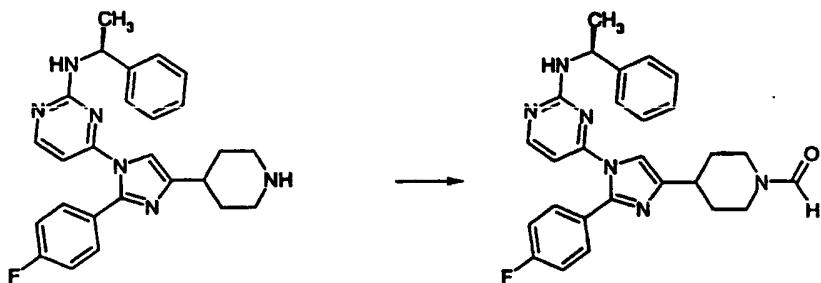
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-ethoxycarbonyl)piperidine-1-yl imidazole (4.4 g; 8.56 mmol) and trimethylsilyliodide (4.4 ml; 32.3 mmol) are dissolved in CHCl<sub>3</sub> (85 ml) and heated at 60 °C for 3 h. After cooling to room temperature, the reaction mixture is acidified with 6M HCl (35 ml) and the water phase washed twice with TBME. The

combined aqueous phases are treated with a saturated solution of  $\text{Na}_2\text{CO}_3$  and extracted twice with methylene chloride. The combined organic phases are washed with a saturated solution of  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness. Purification over  $\text{SiO}_2$  (TBME/MeOH/NH<sub>3</sub>conc 90/9/1 to 79/27/3) yields the title compound as a white foam (3.1 g; 82%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6, 120 C): 1.41 (d, 3H); 1.69-1.82 (dq, 2H); 2.08 (bd, 2H); 2.71-2.81 (bt, 1H); 2.87 (t, 2H); 3.26 (bd, 2H); 4.30-4.40 (m, 1H); 6.30 (d, 1H); 7.10-7.48 (m, 10H); 8.23 (d, 1H).

MS (m/z; ESI): 443.2 (MH<sup>+</sup>).

**Example 53: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-formyl)-piperidine-1-yl imidazole**

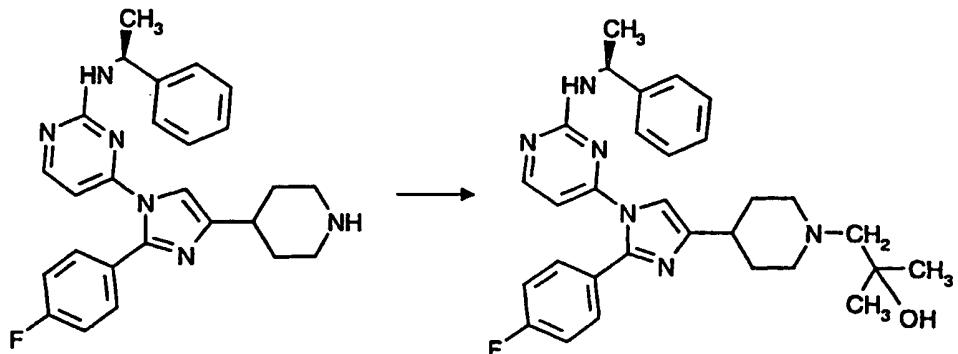


Imidazole (16.2 mg; 0.237 mmol) is dissolved in DMF (0.021 ml; 0.277 mmol) and treated with  $\text{Me}_3\text{SiCl}$  (0.03 ml; 0.237 mmol) for 20 min at room temperature. 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole (35 mg; 0.079 mmol) is dissolved in DMF (0.025 ml) and added to the preformed formylation reagent and stirred at room temperature for 24 h. The reaction mixture is poured on a saturated  $\text{Na}_2\text{CO}_3$  solution and extracted three times with TBME. The combined organic phases are washed with a saturated solution of  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness.

<sup>1</sup>H-NMR (400MHz; DMSO-d6): mixture of rotamers. 1.24-1.58 (m, 5H); 1.97-2.10 (bt, 2H); 2.79 (dt, 1H); 2.85 (bt, 1H); 3.18 (dt, 1H); 3.75 (bd, 1H); 4.21 (bd, 1H); 4.45 (bs, 0.7H); 5.15 (bs, 0.3H); 6.20 (bs, 0.3H); 6.40 (bs, 0.7H); 7.15-7.32 (m, 8H); 7.42 (bt, 2H); 8.01 (d, 1H); 8.05 (s, 1H); 8.28 (bs, 1H).

MS (m/z; ESI): 471.2 (MH<sup>+</sup>).

**Example 54: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole**

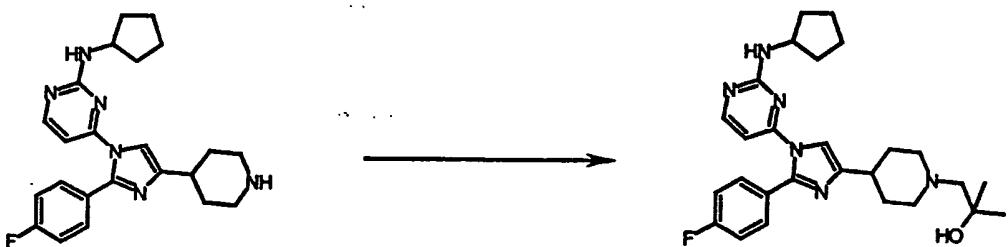


2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole (35 mg; 0.079 mmol) is dissolved in EtOH (0.5 ml) and heated with isobutylene oxide (0.023 ml; 0.31 mmol) at 90 C for 3 h. The reaction mixture is evaporated to dryness and purified via SiO<sub>2</sub> chromatography (TBME/MeOH/NH<sub>3</sub>conc 97/3/0.3 to 96/4/0.4) to yield the title compound as a yellow foam (34 mg; 83%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6) mixture of rotamers. 1.10 (s, 3H); 1.11 (s, 3H); 1.22-1.34 (m, 3H); 1.57-1.71 (m, 2H); 1.83-1.92 (bd, 2H); 2.22 (m, 4H); 3.00 (bd, 2H); 2.43-2.52 (bt, 1H); 4.05 (s, 1H, OH); 4.45 (bs, 1H); 6.18 (bs, 0.3H); 6.40 (bs, 0.7H); 7.13-7.32 (m, 8H); 7.43 (bt, 2H); 8.00 (d, 1H, NH); 8.28 (bs, 1H).

MS (m/z; ESI): 515.3 (MH+, 100); 258 (80).

**Example 55: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole**

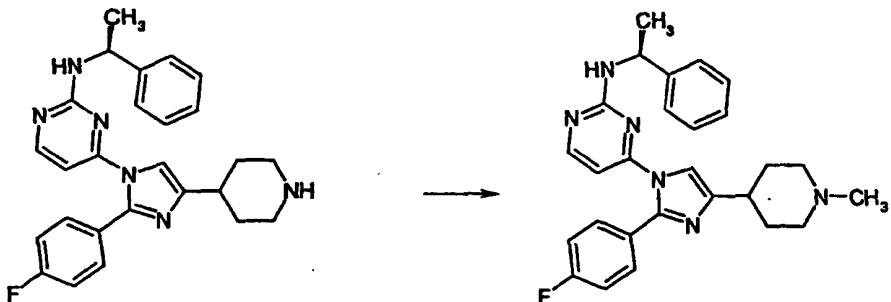


The title compound is prepared according to the procedures described above and is obtained as colorless crystals in 73% yield.

<sup>1</sup>H-NMR (400MHz; DMSO-d6, 180°C): 1.28 (s, 6H); 1.40-1.60 (m, 4H); 1.66-1.76 (m, 2H);

1.80-1.91 (m, 2H); 1.95-2.20 (m, 4H); 2.55-3.00 (m, 5H); 3.30-3.40 (m, 2H); 3.95-4.05 (m, 1H);  
 6.33 (d, 1H); 7.11 (dd, 2H); 7.35 (s, 1H); 7.48 (dd, 2H); 8.25 (d, 1H).  
 MS (m/z; ESI): 479 (MH+, 60); 240 (100); 231 (80).

**Example 56: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-methyl)-piperidine-1-yl imidazole**

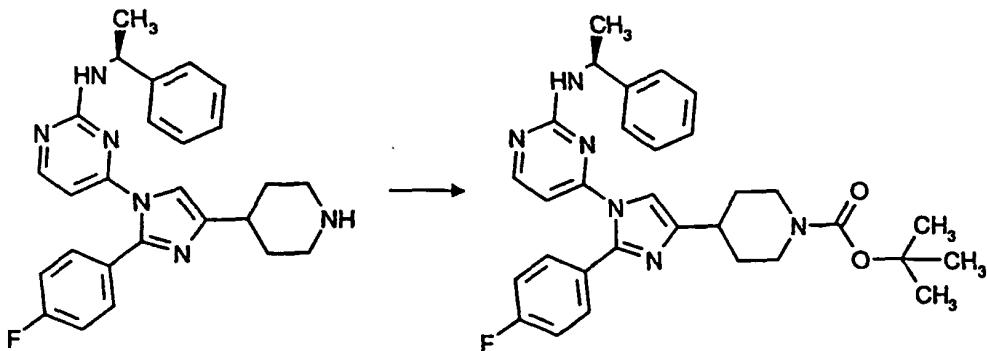


2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole (35 mg; 0.079 mmol) in acetonitrile (0.5 ml) and formaldehyde (35% in water; 0.010 ml; 0.126 mmol) are treated with NaCNBH<sub>3</sub> (6 mg; 0.095 mmol). After stirring for 5 min, HOAc (0.0045 ml; 0.079 mmol) is added and stirring continued for 2 h at room temperature. The reaction mixture is poured on 1N HCl and washed with TBME. The aqueous phase is treated with a saturated solution of Na<sub>2</sub>CO<sub>3</sub> until the pH becomes basic and extracted three times with TBME. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (TBME/MeOH/NH<sub>3</sub>conc 90/9/1) yields the title compound as a white foam (14.6 mg; 40%).

1H-NMR (400MHz; DMSO-d6, 120 C): 1.41 (d, 3H); 1.62-1.74 (dq, 2H); 1.92-2.00 (bd, 2H); 2.12-2.10 (dt, 2H); 2.21 (s, 3H); 2.43-2.52 (bt, 1H); 2.79-2.90 (m, 2H); 4.82-4.91 (m, 1H); 6.29 (d, 1H); 7.11-7.48 (m, 8H); 7.45 (dd, 2H); 8.23 (d, 1H).

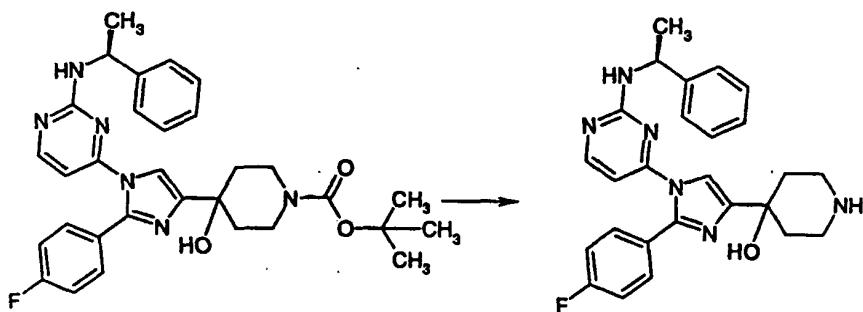
MS (m/z; ESI): 457.2 (MH+, 75); 229.2 (100).

**Example 57: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy-4-tert.butylloxycarbonyl)piperidine-1-yl imidazole**



4-Bromo-2-(4-fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)imidazol (250 mg; 0.57 mmol) is dissolved in THF (3 ml), cooled to -78 C under argon and treated with nBuLi (1.6M solution in hexane; 0.713 ml; 1.14 mmol) at this temperature. After 10 min at -78 C, N-tert.butyloxypiperidine-4-one (114 mg; 0.57 mmol) is added in THF (0.8 ml). Stirring is continued for 5 min at -78 C, then the reaction mixture poured on a saturated solution of NaCl in water and extracted with TBME three times. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (TBME/hexane 1/1 to 8/2) yielded the title compound as a colorless foam (154 mg; 49%).  
<sup>1</sup>H-NMR (400MHz; DMSO-d6, 120 C): 1.41 (d, 3H); 1.49 (s, 9H); 1.76 (bd, 2H); 2.00 (dt, 2H); 3.32 (dt, 2H); 3.60-3.71 (m, 2H); 4.49 (s, 1H, OH); 4.81-4.92 (m, 1H); 6.31 (d, 1H); 7.10-7.22 (m, 4H); 7.23-7.31 (m, 4H); 7.48 (bd, 1H, NH); 7.41-7.50 (m, 2H); 8.25 (d, 1H).  
MS (m/z; ESI): 559.3 (MH+, 100); 541 (15); 503.3 (70); 485.3 (20).

**Example 58: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy)piperidine-1-yl imidazole**

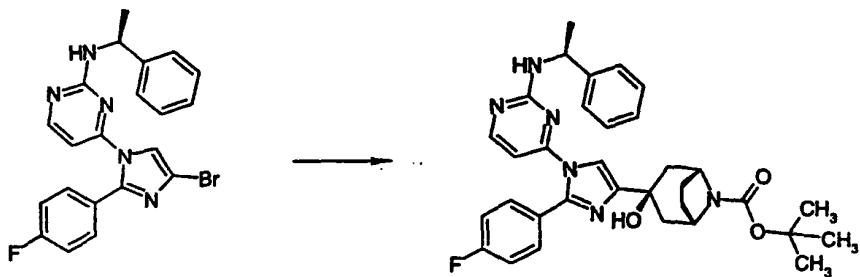


2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy-4-tert.butylloxycarbonyl)piperidine-1-yl imidazole (105 mg; 0.188 mmol) is treated with EtOH/HClconc (4 ml; 1:1) for 10 min at room temperature. The reaction mixture is washed twice with TBME, the aqueous phase is made alkaline by adding a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted three times with TBME. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness, yielding the title compound as a white foam (72 mg; 84%).

<sup>1</sup>H-NMR (400MHz; DMSO-d6) mixture of rotamers. 1.25-1.36 (m, 3H); 1.61 (bd, 2H); 1.95 (bt, 2H); 2.65-2.72 (m, 2H); 2.89 (bt, 2H); 4.48 (bs, 1H); 4.71 (s, 1H, OH); 6.48 (s, 1H); 7.15-7.48 (m, 8H); 7.43 (bs, 2H); 8.02 (d, 1H, NH); 8.28 (s, 1H).

MS (m/z; ESI): 459.2 (MH<sup>+</sup>, 100); 360.1 (10); 250.7 (50); 230.1 (60).

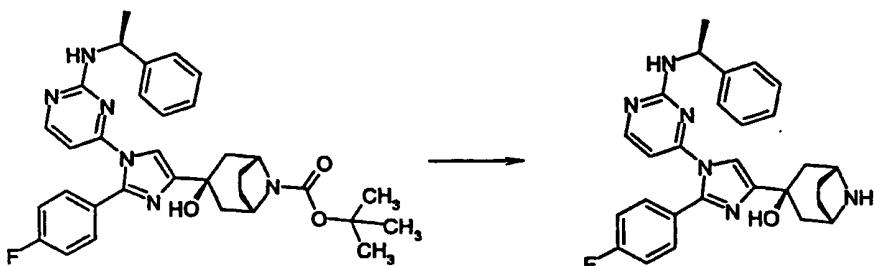
**Example 59: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-N-tert.butylloxycarbonylnortropan-3b-yl) imidazole**



4-Bromo-2-(4-fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)imidazol (150 mg; 0.342 mmol) is dissolved in THF (3 ml), cooled to -78 C under argon and treated with nBuLi (1.6M solution in hexane; 0.428 ml; 0.685 mmol) at this temperature. After 10 min at -78 C, N-tert. Butyloxy nortropinone (77 mg; 0.34 mmol) is added in THF (0.8 ml). Stirring is continued for 5 min at -78 C, then the reaction mixture poured on a saturated solution of NaCl in water and extracted with TBME three times. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (acetone/hexane 15/85) yields the title compound as a colorless foam (67 mg; 34%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>) NMR mixture of rotamers. 1.31 (bs, 3H); 1.43 (s, 9H); 1.68-1.88 (m, 4H); 2.21-2.49 (m, 4H); 4.11 (bs 2H); 4.50 (bs, 1H); 4.97 (s, 1H, OH); 6.18 (bs, 0.3H); 6.48 (bs, 0.7H); 7.15-7.35 (m, 8H); 7.37-7.45 (m, bt, 2H); 8.20 (bs, 1H); 8.28 (bs, 1H).  
MS (m/z; ESI): 585.3 (MH<sup>+</sup>, 100).

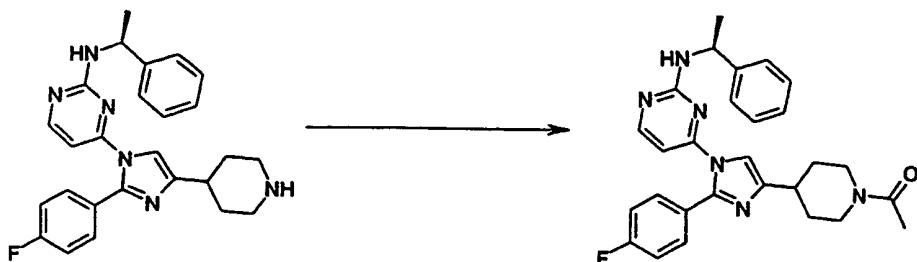
**Example 60: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-nortropan-3b-yl) imidazole**



2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-N-tert.butyloxycarbonylnortropan-3b-yl) imidazole (54 mg; 0.098 mmol) is dissolved in EtOH/HClconc (4 ml; 1:1) and stirred at room temperature for 10 min. Water is added and the aqueous phase washed once with TBME, adjusted to pH >10 by adding a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted three times with TBME. The combined organic phases were washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to yield the title compound as a white foam (44 mg; 98%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>) NMR mixture of rotamers. 1.23-1.48 (m, 3H); 1.58-1.66 (M, 2H); 1.77 (d, 2H); 2.18 (bd, 2H); 2.22 (d, 2H); 3.41 (bs, 2H); 4.48 (bs, 1H); 4.63 (s, 1H, OH); 6.13 (bs, 0.3H); 6.48 (bs, 0.7); 7.16 (m, 8H); 7.40-7.47 (bt, 2H); 8.00 (d, 1H); 8.26 (bs, 1H).  
MS (m/z; ESI): 485 (MH<sup>+</sup>, 100); 284.3 (20); 263.7 (10).

**Example 61: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-acetyl)piperidine-1-yl imidazole**



2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole (20 mg; 0.045 mmol) dissolved in THF (0.5 ml), NEt<sub>3</sub> (0.006 ml; 0.045 mmol) and DMAP (0.5 mg; 0.0045 mmol) is treated with acetylchloride (0.0032 ml; 0.045 mmol) for 10 min at room temperature. The reaction mixture poured on a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with TBME three times. The combined organic phases are washed with a saturated solution of NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. Purification over SiO<sub>2</sub> (acetone/hexane 1/1 to 1/0) yields the title compound as a colorless solid (12 mg; 57%).

<sup>1</sup>H-NMR (400MHz; DMSO-d<sub>6</sub>, 120 C): 1.42 (d, 3H); 1.51-1.67 (bq, 2H); 1.99 (bs, 2H); 2.05 (s, 3H); 2.88 (bs, 1H); 3.02 (bs, 2H); 3.95-4.20 (bs, 2H); 4.30-4.40 (m, 1H); 6.30 (d, 1H); 7.10-7.32 (m, 8H); 7.35 (d, 1H, NH); 7.45 (dd, 2H); 8.25 (d, 1H).

MS (m/z; ESI): 485.3 (MH<sup>+</sup>).

The Agents of the Invention, as defined above, e.g., of formula I, particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF- $\alpha$  and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in *E. coli*) is coated onto the wells of microtiter plates (50 µl/well; 1 µg/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 µl aliquots to a final reaction volume of 50 µl.

1. Agents of the Invention titrated from 10 to 0.001 µM in 10-fold dilutions or solvent (DMSO) or H<sub>2</sub>O.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β-glycerophosphate (Sigma #G-6251); 125 mM MgCl<sub>2</sub> (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.
3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in *E. coli*)
4. cold ATP (final concentration 120 µM; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 µl/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.
2. Biotin labelled goat-anti-rabbit IgG (50 µl/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 µl/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084 ) for 30 min at RT.
4. Substrate (100 µl/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + MgCl<sub>2</sub>.6H<sub>2</sub>O (100 mg/l; Merck #5833) + Na Azide (0.2 g/l) + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength

mode (measurement filter 405 nm and reference filter 490 nm). The background value (without ATP) is subtracted and IC<sub>50</sub> values are calculated using the Origin computer program (4 parameter logistic function).

Agents of the Invention typically have IC<sub>50</sub>s for p38 MAP kinase inhibition in the range from about 100 nM to about 10 nM or less when tested in the above assay. For example the compounds of Examples 9, 14, 15, 18-23, 30-33, 35, 49, 51, 52 and 55-57 have IC<sub>50</sub>s for p38 MAP kinase inhibition in the range from about 1 nM to about 10 nM when tested in the above assay.

#### Assay for Inhibition of TNF- $\alpha$ release from hPBMCs

Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145: 105. and used at a concentration of 10<sup>5</sup> cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFNg (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF- $\alpha$  in the supernatant is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Invention typically suppress TNF release in this assay with an IC<sub>50</sub> of from about 500 nM to about 10 nM or less when tested in this assay. For instance the compounds of Examples 4, 8, 9, 19, 20, 23, 31-33, 35 and 49-57, 59 and 60 have IC<sub>50</sub>s in the range from about 10 nM to about 1 nM.

#### Assay for Inhibition of TNF- $\alpha$ Production in LPS stimulated mice

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF- $\alpha$ ) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF- $\alpha$ . Using 20 mg/kg of LPS levels of up to 15 ng of TNF- $\alpha$  / ml

plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

As indicated in the above assays Agents of the Invention are potent inhibitors of TNF- $\alpha$  release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNF $\alpha$  and IL-1, e.g., inflammatory conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progradiente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung-fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNFa, e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS -related cachexia, e.g., associated with or consequential to HIV infection.

Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of Novel Compound administered orally once or, more suitably, in divided dosages two to four times/day.

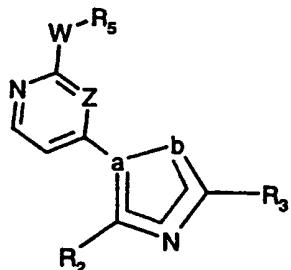
The Novel Compounds may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Novel Compounds may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg Novel Compound per unit dosage.

In accordance with the foregoing the present invention also provides in a further series of embodiments:

- A. A method of inhibiting production of soluble TNF, especially TNF $\alpha$ , or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.
- B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
- C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
- D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

CLAIMS

## 1. A compound of formula I



wherein

a is N or C;

b is CH when a is N, or O when a is C;

       denotes a single or a double bond dependent upon whether the azole ring is an imidazole or an oxazole ring;

Z is N or CH;

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond ;

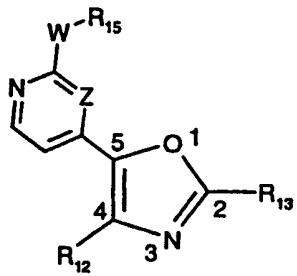
R<sub>2</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, or NH<sub>2</sub> which is optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted;

R<sub>3</sub> is H, halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or methylenearminoguanidinyl (i.e. -CH=N-NH-C(NH).NH<sub>2</sub>), each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocycl containing from 5 to 7 ring atoms and optionally containing a further hetero atom;

R<sub>5</sub> is C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or C<sub>3</sub>-C<sub>12</sub>cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl, halogen, halo-

substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, or optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,  
or an ester thereof or acid addition salt thereof.

## 2. A compound of formula II



II

wherein

Z is N or CH;

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond;

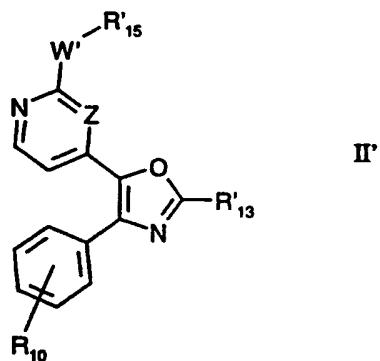
R<sub>12</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, or NH<sub>2</sub> which is optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted;

R<sub>13</sub> is H, halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or methyleneaminoguanidinyl (i.e. -CH=N-NH-C(NH).NH<sub>2</sub>), each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, halo-substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, optionally mono-or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom;

R<sub>15</sub> is C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, or C<sub>3</sub>-C<sub>12</sub>cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl, halogen, halo-

substituted-C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,  
and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

3. A compound according to claim 2 of formula II'



wherein

R<sub>15</sub>' is phenyl or C<sub>3</sub>-C<sub>7</sub>cycloalkyl each of which is optionally mono-substituted by halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>10</sub>alkoxy, hydroxy, trihalomethyl or -NR<sub>7</sub>R<sub>8</sub>, where R<sub>7</sub> and R<sub>8</sub> are independently H, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>6</sub>-C<sub>10</sub>aryl, C<sub>6</sub>-C<sub>10</sub>heteroaryl, C<sub>7</sub>-C<sub>11</sub>aralkyl or C<sub>7</sub>-C<sub>11</sub>heteroaralkyl;

R<sub>10</sub> is halogen, CF<sub>3</sub>, cyano, amido, thioamido, amino C<sub>1</sub>-alkyl;

R<sub>13</sub>' is H, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, phenyl, pyridyl, morpholinyl, piperidinyl, piperazinyl, or N-mono- or di-C<sub>1</sub>-C<sub>4</sub>alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted by hydroxy, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, carboxy, optionally C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>alkoxy substituted carbonyl, or optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub>alkyl substituted amino;

Z is N or CH and

W' is -NH-Y'-, -O- or -S-, where Y' is -CH<sub>2</sub>- , -CH<sub>2</sub>-CH<sub>2</sub>- , -CH(CH<sub>3</sub>)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

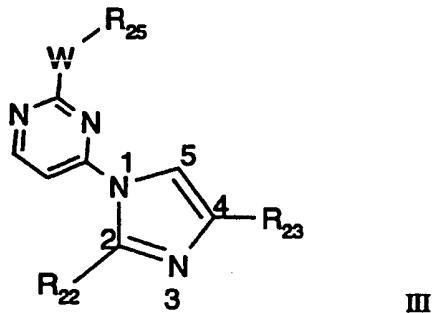
4. A compound according to claim 2 selected from:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-morpholinylloxazole;

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N-piperidinyloxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-ethoxy-carbonylpiperazin-1-yl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-methyl-piperidine-1-yl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-ethyl-piperazin-1-yl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-N,N-diethyl-aminooxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-N-acetyl-piperidine-1-yl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-piperazinyl) oxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-amino-1-methyl)ethyloxazole;  
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)-2-(1-hydroxy-4-methylpiperidine-1-yl)oxazole;  
4-(4-Fluorophenyl)-2-(1-hydroxy-4-methyl)piperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propyl)piperidine-1-yl)-5-(2-cyclopropylmethylamino-4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-5-(2-cyclopropylmethylamino-4-pyrimidyl)-2-(4-NH-piperidine-1-yl)oxazole;  
4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidin-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole;  
4-(4-Fluorophenyl)-2-(1-hydroxy-4-ethyl)piperidin-1-yl)-5-(2-cyclopropylamino-4-

pyridyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidin-1-yl)-5-(2-cyclopropylamino-4-pyridyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)oxazole;  
 4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-cyclohexylamino-4-pyridyl)oxazole, and  
 4-(4-Fluorophenyl)-2-(4-N-(2-hydroxy-2-methyl)propylpiperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridyl)oxazole.

5. A compound according to claim 1 of formula III



wherein

W is -NR<sub>6</sub>-Y-, -O- or -S-,

where R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkylC<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl, C<sub>7</sub>-C<sub>19</sub>aralkyl or C<sub>4</sub>-C<sub>19</sub>heteroaralkyl, and -Y- is C<sub>1</sub>-C<sub>4</sub>alkylene or a direct bond;

R<sub>22</sub> is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF<sub>3</sub>, cyano, amido or thioamido, carboxylate or thiocarboxylate, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, or NH<sub>2</sub> which is optionally mono- or di-N-C<sub>1</sub>-C<sub>4</sub> alkyl substituted;

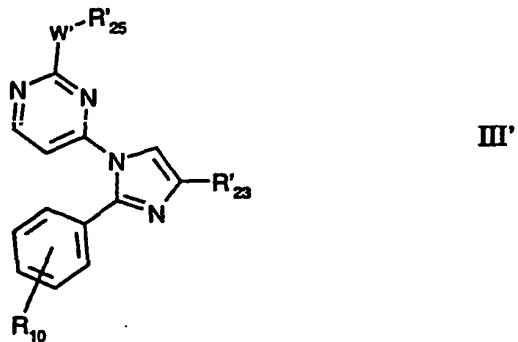
R<sub>23</sub> is H, halogen, C<sub>1</sub>-C<sub>10</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>18</sub>heterocycloalkyl, C<sub>6</sub>-C<sub>18</sub>aryl, C<sub>3</sub>-C<sub>18</sub>heteroaryl or methyleneaminoguanidinyl (i.e. -CH=N-NH-C(NH)NH<sub>2</sub>), each of which may be optionally substituted by up to 4 substituents separately selected from C<sub>1</sub>-

$C_4$ alkyl optionally substituted by hydroxy, halogen, halo-substituted- $C_1$ - $C_4$ alkyl, hydroxy,  $C_1$ - $C_4$ alkoxy,  $C_1$ - $C_4$ alkylthio, carboxy, or optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, optionally mono-or di-N- $C_1$ - $C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom;

$R_{25}$  is  $C_6$ - $C_{18}$ aryl,  $C_3$ - $C_{18}$ heteroaryl, or  $C_3$ - $C_{12}$ cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from  $C_1$ - $C_4$ alkyl, halogen, halo-substituted- $C_1$ - $C_4$ alkyl, hydroxy,  $C_1$ - $C_4$ alkoxy,  $C_1$ - $C_4$ alkylthio, or optionally mono-or di-N- $C_1$ - $C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,

and pharmaceutically-acceptable and -cleavable ester thereof or acid addition salts thereof.

6. A compound according to claim 1, of formula III'



wherein

$R'_{25}$  is phenyl or  $C_3$ - $C_7$ cycloalkyl each of which is optionally mono-substituted by halogen,  $C_1$ - $C_{10}$ alkyl,  $C_1$ - $C_{10}$ alkoxy, hydroxy, trihalomethyl or -NR<sub>7</sub>R<sub>8</sub>, where R<sub>7</sub> and R<sub>8</sub> are independently H,  $C_1$ - $C_6$ alkyl,  $C_6$ - $C_{10}$ aryl,  $C_6$ - $C_{10}$ heteroaryl,  $C_7$ - $C_{11}$ aralkyl or  $C_7$ - $C_{11}$ heteroaralkyl;

$R'_{10}$  is halogen, CF<sub>3</sub>, cyano, amido, thioamido, amino or  $C_1$ - $C_6$ alkyl;

$R'_{23}$  is H, halogen,  $C_1$ - $C_6$ alkyl, vinyl, phenyl, pyridyl, pyrimidyl, benzofuryl, furyl, thiényl, morpholinyl, piperidinyl, nortropanyl, piperazinyl, methyleneaminoguanidinyl or N-mono- or di- $C_1$ - $C_4$ alkylamino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from  $C_1$ - $C_4$ alkyl optionally substituted by hydroxy, halogen, hydroxy,  $C_1$ - $C_4$ alkoxy, carboxy, optionally  $C_1$ - $C_6$ alkyl or  $C_1$ - $C_6$ alkoxy substituted carbonyl, optionally mono-or di-N- $C_1$ - $C_4$ alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, and

W' is -NH-Y'-, -O- or -S-, where Y' is -CH<sub>2</sub>- , -CH<sub>2</sub>-CH<sub>2</sub>- , -CH(CH<sub>3</sub>)- or a direct bond, or a pharmaceutically-acceptable and -cleavable ester thereof or an acid addition salt thereof.

7. A compound according to claim 5 selected from

- 3-Bromo-2-(4-fluorophenyl)-1-(2-[1-(S)-phenylethyl]amino-4-pyrimidyl)imidazole;
- 4-Bromo-2-(4-fluoromethylphenyl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole;
- 4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole;
- 4-Bromo-2-(3-trifluoromethylphenyl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole;
- 2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-vinylimidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(4-pyridyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-pyridyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(3-pyridyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-thienyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-furyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-amino)pyrimidylimidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-hydroxy)pyrimidylimidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl) 4-(2-N-morpholinyl)pyrimidylimidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-thienyl)-imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(2-benzofuryl)imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(5-chlorothiophen-2-yl)imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-methoxyphenyl)imidazole;
- 2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(4-fluorophenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chloro-4-fluorophenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-(3-chlorophenyl)imidazole;

2-(4-Fluorophenyl)-1-(2-[1-(S)-phenyl-ethyl]amino-4-pyrimidyl)-4-methyleneaminoguanidinyl-imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-ethoxycarbonyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-formyl)-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-methyl)-piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy-4-tert.butyloxycarbonyl)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(1-hydroxy)piperidine-1-yl imidazole;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-N-tert.butyloxycarbonylnortropan-3b-yl) imidazole;

2-(4-Fluorophenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclohexylamino-4-pyrimidyl)imidazole;

2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopropylamino-4-pyrimidyl)imidazole;

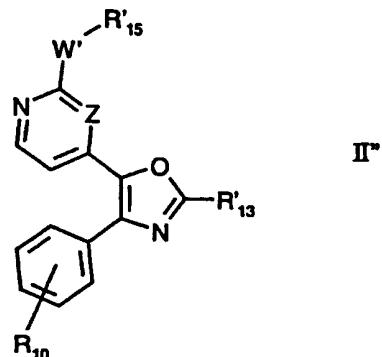
2-(3-Trifluoromethylphenyl)-4-(1-methyl-4-hydroxypiperidin-4-yl)-1-(2-cyclopentylamino-4-pyrimidyl)imidazole;

2-(4-Fluorophenyl)-1-(2-cyclopentyl)amino-4-pyrimidyl)-4-(4-(2-hydroxy-2-methyl)propyl)piperidine-1-yl imidazole;

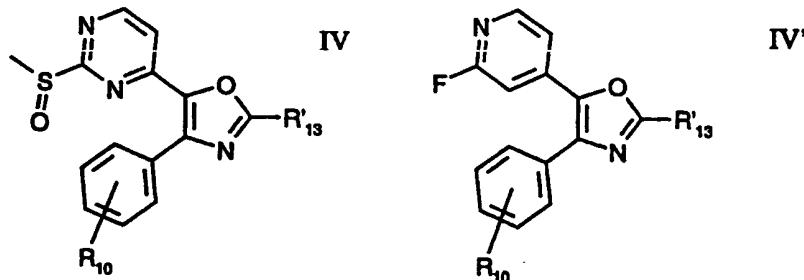
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(3a-hydroxy-nortropan-3b-yl) imidazole, and

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidyl)-4-(4-acetyl)piperidine-1-yl imidazole.

8. A process for the preparation of a compound of formula II''

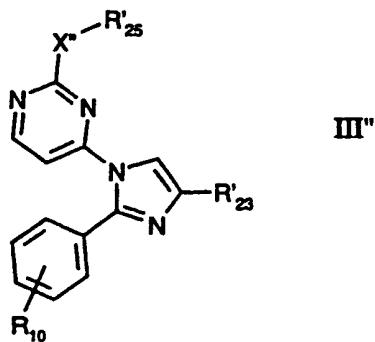


wherein R'13, R'15, R<sub>10</sub> and Z are as defined in claim 3 and W' is -NH-, which comprises reacting the corresponding precursor compound of formula IV or IV'



wherein R'13, R<sub>10</sub> and Z are as defined in claim 3, with the corresponding R'15-NH<sub>2</sub> amine, and thereafter, if desired, converting the compound of formula II'' obtained into a further compound of formula II''' or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

9. A process for the preparation of a compound of formula III''



wherein R'<sub>23</sub>, R'<sub>25</sub> and R<sub>10</sub> are as defined in claim 3 and X'' is -NH- or -O-, comprising reacting a corresponding compound of formula III' in which R'<sub>23</sub> is halogen, e.g. Br, with the corresponding R'<sub>23</sub> ketone or activated R'<sub>23</sub> precursor, e.g. tri-alkylstannyl activated R'<sub>23</sub> precursor, and thereafter, if desired, converting the compound of formula III' obtained into a further compound of formula III" or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

10. A compound according to claim 1 for use as a pharmaceutical.
11. A method of inhibiting production of soluble TNF, especially TNF $\alpha$ , or of reducing inflammation in a subject in need of such treatment which method comprises administering to said subject an effective amount of a compound according to claim 1.
12. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier.
13. Use of a compound according to claim 1 in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent.

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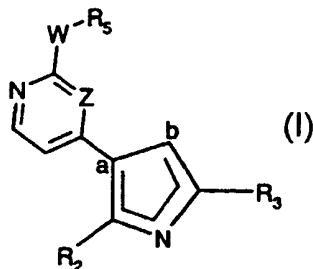
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(75) Inventors/Applicants (*for US only*): RÉVÉSZ, László [CH/CH]; Ob dem Fichtenrain 7, CH-4106 Therwil (CH). SCHLAPBACH, Achim [DE/DE]; Huenerbergweg 8, D-79539 Lörrach (DE).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED AZOLES



(57) Abstract: Compounds of formula (I) wherein the symbols have meaning as defined herein, are p38 MAP kinase inhibitors, and are useful pharmaceutically for treating TNF $\alpha$  and IL-1 mediated diseases, such as rheumatoid arthritis, and diseases of bone metabolism, e.g. osteoporosis.

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP 00/03290

|  |   |  |
|--|---|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b>   |   |  |
| IPC 7 C07D403/04 C07D403/14 C07D401/14 C07D413/04 C07D413/14<br>C07D405/14 C07D409/14 A61K31/506 A61P29/00   |   |  |
| According to International Patent Classification (IPC) or to both national classification and IPC  |   |  |
| <b>B. FIELDS SEARCHED</b>  |   |  |
| Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C07D A61K A61P  |   |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  |   |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br><b>CHEM ABS Data, PAJ</b>  |   |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>  |   |  |
| Category   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
| A  | WO 95 13067 A (SMITH-KLINE)<br>18 May 1995 (1995-05-18)<br>page 1; claims<br>-----<br>US 5 739 143 A (J.LEROY ADAMS)<br>14 April 1998 (1998-04-14)<br>the whole document<br>----- | 1,2,<br>10-13<br>1,5,6,<br>10-13   |
| <input type="checkbox"/> Further documents are listed in the continuation of box C.  |   | <input checked="" type="checkbox"/> Patent family members are listed in annex. |
| <b>* Special categories of cited documents :</b><br>*A* document defining the general state of the art which is not considered to be of particular relevance<br>*E* earlier document but published on or after the international filing date<br>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>*O* document referring to an oral disclosure, use, exhibition or other means<br>*P* document published prior to the international filing date but later than the priority date claimed  |   |  |
| *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>*8* document member of the same patent family |   |  |
| Date of the actual completion of the international search  |   | Date of mailing of the international search report                             |
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| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.<br>Fax: (+31-70) 340-3016   |   | Authorized officer<br><b>Francois, J</b>                                       |

## INTERNATIONAL SEARCH REPORT

... International application No.  
PCT/EP 00/03290

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

|                 |                         |
|-----------------|-------------------------|
| Int'l           | Regional Application No |
| PCT/EP 00/03290 |                         |

| Patent document cited in search report |   | Publication date |  | Patent family member(s)  |  | Publication date   |
|--|---|------------------|--|--|--|--|
| WO 9513067                             | A | 18-05-1995       |  | EP 0727998 A<br>JP 9505055 T   |  | 28-08-1996<br>20-05-1997   |
| US 5739143                             | A | 14-04-1998       |  | US 5658903 A<br>AU 5703398 A<br>EP 0961618 A<br>US 5869660 A<br>WO 9825619 A<br>AU 699646 B<br>AU 6272696 A<br>BR 9608591 A<br>CA 2223533 A<br>CN 1192147 A<br>CZ 9703925 A<br>EP 0831830 A<br>HU 9802259 A<br>JP 11513017 T<br>NO 975716 A<br>PL 323916 A<br>WO 9640143 A |  | 19-08-1997<br>03-07-1998<br>08-12-1999<br>09-02-1999<br>18-06-1998<br>10-12-1998<br>30-12-1996<br>05-01-1999<br>19-12-1996<br>02-09-1998<br>16-09-1998<br>01-04-1998<br>28-09-1999<br>09-11-1999<br>04-02-1998<br>27-04-1998<br>19-12-1996 |